IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): LEXICON GENETICS INCORPORATED

Application No.: 09/769,952

Filed: January 25, 2001

Group Art Unit:Unknown

Examiner: Unknown

Title: Novel Human Enzymes and Polynucleotides Encoding the Same

Attorney Docket No.: LEX-0118-PCT

PETITION UNDER 37 C.F.R. § 1.182

BOX DAC
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

The present petition is being filed by the Applicants to request that the Patent and Trademark Office (PTO) provide an appropriate serial number to a **PCT application** (Applicant docket number **LEX-0118-PCT**) filed by Applicants on January 25, 2001. The present petition is deemed necessary because the PTO has apparently accorded the above-identified **PCT** application with a **U.S.** Patent Application Serial Number. While considering the present petition, please consider the following summary of the relevant facts:

On January 25, 2001, Applicants mailed a package to the PTO that contained two separate patent applications. The first application was the presently described PCT application and, as evidenced by the complete copy of the filed materials-- Exhibit A, was clearly directed to "Box PCT." The second application was a U.S. nonprovisional application (that generally corresponded to the U.S. version of the PCT application, a complete copy of the U.S. application as filed is provided as Exhibit B) that was clearly directed to "Box Patent Application." On February 8, 2001, Applicants received a stamped received postcard verifying the PTO's receipt of the PCT application (Exhibit C), and a separate stamped received postcard for U.S. nonprovisional patent application (Exhibit D). Upon inspection of the postcards, it became apparent to Applicants' representative that the presently described **PCT application** (Atty. docket number **LEX-0118-PCT**) had been erroneously accorded a

U.S. Serial Number (09/769,952). In fact, the same serial number was apparently accorded to the corresponding U.S. nonprovisional application (Atty docket number **LEX-0118-USA)** and the PCT application at issue.

As shown in the stamped received postcard for the PCT application (Exhibit D), the postcard was clearly marked **Box PCT** [bold in original] and, when filed, the postcard had been attached to a complete PCT Application filed in conjunction with a PCT Request, PCT (Annex - Fee Calculation Sheet), and a PCT Power of Attorney (Exhibit A). There were also two computer diskettes submitted. One of these diskettes was clearly marked both on the disk label and the disk mailer as "PCT Easy" along with the attorney docket number (LEX-0118-PCT). The second diskette was clearly marked both on the disk label and disk mailer as "Sequence Listing" along with the attorney docket number (LEX-0118-PCT). After contacting the PCT Help Desk, Applicants' representative was able to confirm that the PTO had apparently placed **the same U.S. Patent Application Serial Number** on the presently described PCT application **and** the related U.S. nonprovisional application that had been mailed along with the PCT application at issue. From what Applicants' representative and the PCT help desk could surmise from the PTO files, it appears that the PTO had apparently erroneously assumed that the Utility Application Transmittal sheet from the U.S. nonprovisional application somehow related to both the U.S. application and the separate PCT application and mistakenly combined both the presently described **PCT** application and the **U.S.** nonprovisional application. In fact, Applicants have been informed that both the PCT application at issue and the U.S. nonprovisional application have been mistakenly placed in the same file (for the U.S. application) at the PTO. Applicants also note that, according to the PCT Help Desk, the computer diskettes received by the PTO are apparently missing from the file. Given the rather unusual nature of the present predicament, the PCT Help Desk has also informed Applicants' representative that the present situation can only be rectified by Applicants filing the present petition.

Accordingly, the Applicants hereby petition the PTO to remove the presently described PCT application from the U.S. application file, forward the complete PCT Application identifiable by Atty Docket Number LEX-0118-PCT to the appropriate office

(Box PCT), and accord the above identified PCT Application with an International Application Number with the filing date of January 25, 2001.

The Commissioner is authorized to charge the requisite Petition Fee under 37 C.F.R. section 1.17(h) to Deposit Account No. 50-0892, or for any matter in connection with this Petition, which may be required.

Respectfully submitted,

3/09/01
Date

Lance K. Ishimoto Reg. No. 41,866
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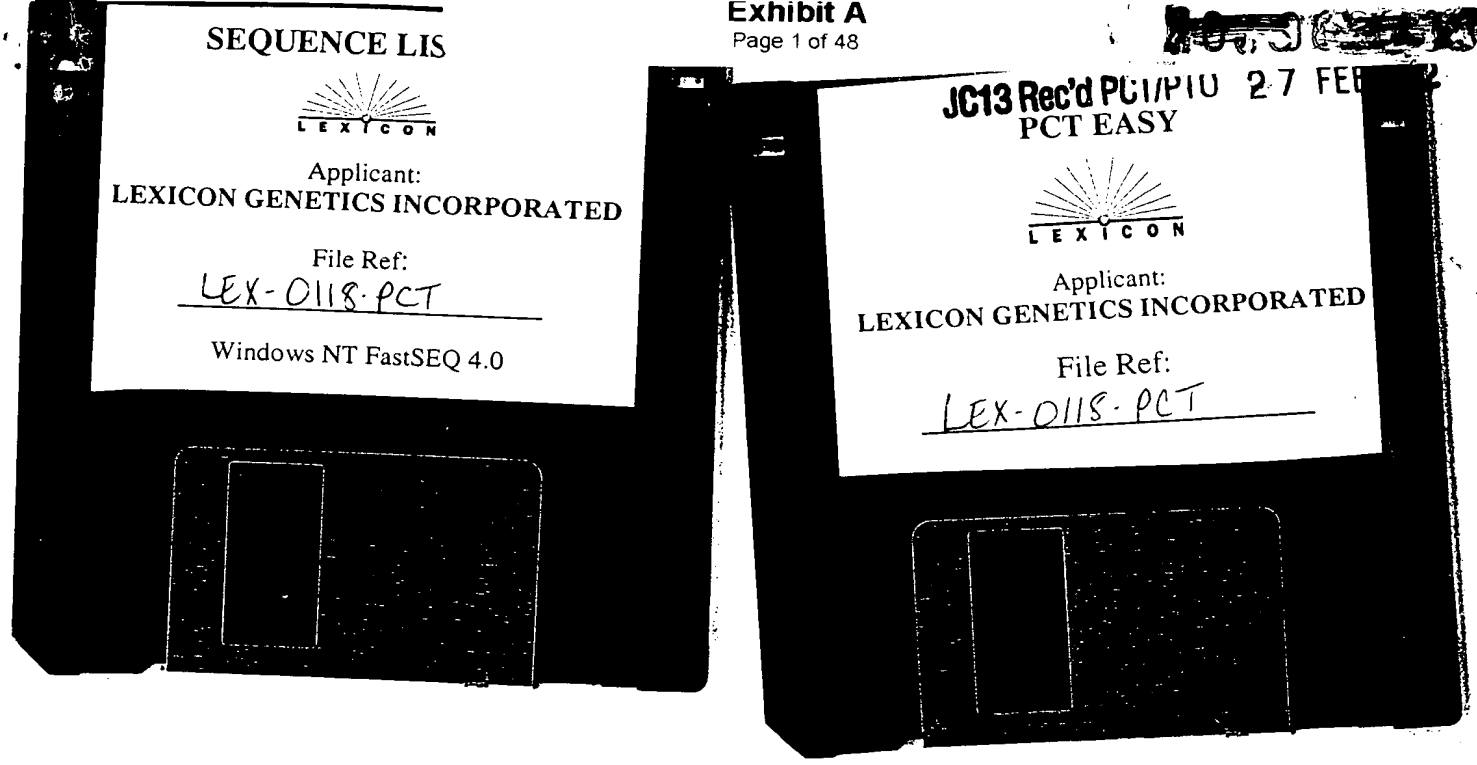

Box PCT
Express Mail No.: EL 672 756 762 US
Date Mailed: January 25 2000 Int'l. Appl. Ser. No.: to be assigned
Applicant: Lexicon Genetics Incorporated
Title: Novel Human Enzymes and Polynucleotides Encoding the Same
Attorney Docket No.: LEX-0118-PCT

X Specification 28 pages total (26 pages spec; 1 claim page(s); 1 page Abstract)
X Request Form 5 pages
X Power of Attorney executed
X Fee Calculation Sheet
X Verified Statement executed
___ Drawings (___ pages; ___ number of drawings)
X Sequence Listing (8 pages; X machine-readable data carrier)
___ PCT-EASY diskette
Other: return postcard;

PCT REQUEST

LEX-0118-PCT

Original (for **SUBMISSION**) - printed on 25.01.2001 11:08:45 AM

0	**For receiving Office use only**	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	

0-4	**Form - PCT/RO/101 PCT Request**	
0-4-1	Prepared using	PCT-EASY Version 2.91 (updated 01.01.2001)
0-5	**Petition**	
	The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	**Receiving Office (specified by the applicant)**	United States Patent and Trademark Office (USPTO) (RO/US)
0-7	**Applicant's or agent's file reference**	LEX-0118-PCT
I	**Title of invention**	NOVEL HUMAN ENZYMES AND POLYNUCLEOTIDES ENCODING THE SAME
II	**Applicant**	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States
II-4	Name	LEXICON GENETICS INCORPORATED
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II-7	State of residence	US
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II-9	Facsimile No.	281-364-0155
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III-2-1	This person is:	inventor only
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PCT REQUEST

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IV-1	**Agent or common representative; or address for correspondence** The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	ISHIMOTO, Lance, K.
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IV-1-4	Facsimile No.	281-364-0155
IV-1-5	e-mail	lkishimoto@lexgen.com
IV-2	**Additional agent(s)**	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	SEFERIAN, Peter, G.
V	**Designation of States**	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW

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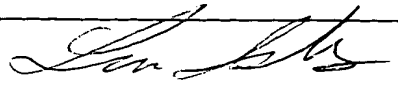
V-5	**Precautionary Designation Statement** In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.		
V-6	**Exclusion(s) from precautionary designations**	NONE	
VI-1	**Priority claim of earlier national application**		
VI-1-1	Filing date	28 January 2000 (28.01.2000)	
VI-1-2	Number	60/179,000	
VI-1-3	Country	US	
VI-2	**Priority document request** The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1	
VII-1	**International Searching Authority Chosen**	European Patent Office (EPO) (ISA/EP)	
VIII	**Check list**	number of sheets	electronic file(s) attached
VIII-1	Request	5	-
VIII-2	Description (excluding sequence listing part)	26	-
VIII-3	Claims	1	-
VIII-4	Abstract	1	EZABST00.TXT
VIII-5	Drawings	0	-
VIII-6	Sequence listing part of description	8	-
VIII-7	TOTAL	41	
	Accompanying items	paper document(s) attached	electronic file(s) attached
VIII-8	Fee calculation sheet	✓	-
VIII-9	Separate signed power of attorney	✓	-
VIII-15	Nucleotide and/or amino acid sequence listing in computer readable form		separate diskette
VIII-16	PCT-EASY diskette	-	diskette
VIII-17	Other (specified):	Verified Statement	-
VIII-17	Other (specified):	return postcard	-
VIII-18	**Figure of the drawings which should accompany the abstract**		
VIII-19	**Language of filing of the international application**	English	

IX-1	Signature of applicant or agent	
IX-1-1	Name (LAST, First)	ISHIMOTO, Lance, K. Reg No. 41,866

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	

PCT REQUEST

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Original (for SUBMISSION) - printed on 25.01.2001 11:08:45 AM

III-3	Applicant and/or inventor	
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III-8	Applicant and/or inventor	
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NOVEL HUMAN ENZYMES AND POLYNUCLEOTIDES ENCODING THE SAME

The present application claims the benefit of U.S. Provisional Application Number 60/179,000 which was filed on January 28, 2000 and is herein incorporated by reference in its entirety.

1. INTRODUCTION

The present invention relates to the discovery, identification, and characterization of novel human polynucleotides encoding proteins sharing sequence similarity with mammalian enzymes. The invention encompasses the described polynucleotides, host cell expression systems, the encoded protein, fusion proteins, polypeptides and peptides, antibodies to the encoded proteins and peptides, and sequencetically engineered animals that either lack or over express the disclosed sequences, antagonists and agonists of the proteins, and other compounds that modulate the expression or activity of the proteins encoded by the disclosed polynucleotides that can be used for diagnosis, drug screening, clinical trial monitoring and the treatment of physiological disorders.

2. BACKGROUND OF THE INVENTION

Enzymes are biological catalysts that modify biological substrates, including proteins, as part of degradation, maturation, catabolic, metabolic, differentiation, and secretory pathways within the body. Enzyme abnormalities have thus been associated with, *inter alia*, growth, development, protein and cellular senescence, cancer, or other diseases.

3. SUMMARY OF THE INVENTION

The present invention relates to the discovery, identification, and characterization of nucleotides that encode

novel human proteins, and the corresponding amino acid sequences of these proteins. The novel human proteins (NHPs) described for the first time herein share structural similarity with nitrilase proteins from a wide variety of living organisms.

The novel human nucleic acid (cDNA) sequences described herein, encode proteins/open reading frames (ORFs) of 276, 159, 121, 168, 130, 152, and 285 amino acids in length (see respectively SEQ ID NOS: 2, 4, 6, 8, 10, 12 and 14).

The invention also encompasses agonists and antagonists of the described NHPs including small molecules, large molecules, mutant NHPs, or portions thereof that compete with native NHPs, NHP peptides, and antibodies, as well as nucleotide sequences that can be used to inhibit the expression of the described NHPs (*e.g.*, antisense and ribozyme molecules, and gene or regulatory sequence replacement constructs) or to enhance the expression of the described NHPs (*e.g.*, expression constructs that place the described sequence under the control of a strong promoter system), and transgenic animals that express a NHP transgene, or "knock-outs" (which can be conditional) that do not express a functional NHP.

Further, the present invention also relates to processes for identifying compounds that modulate, *i.e.*, act as agonists or antagonists, of NHP expression and/or NHP activity that utilize purified preparations of the described NHP and/or NHP product, or cells expressing the same. Such compounds can be used as therapeutic agents for the treatment of any of a wide variety of symptoms associated with biological disorders or imbalances.

4. DESCRIPTION OF THE SEQUENCE LISTING AND FIGURES

The Sequence Listing provides the sequences of the NHP ORFs encoding the described NHP amino acid sequences. SEQ ID NOS:15 describe representative a nitrilase-like ORF with flanking sequences.

5. DETAILED DESCRIPTION OF THE INVENTION

The NHPs, described for the first time herein, are novel proteins that are expressed in, *inter alia,* human cell lines, gene trapped cells and human brain, fetal brain, pituitary, cerebellum, spinal cord, thymus, spleen, lymph node, bone marrow, trachea, lung, kidney, fetal liver, liver, prostate, testis, thyroid, adrenal gland, pancreas, salivary gland, stomach, small intestine, colon, skeletal muscle, heart, placenta, mammary gland, adipose, skin, esophagus, bladder, pericardium, hypothalamus, ovary, fetal kidney, and fetal lung cells.

The described sequences were compiled from gene trapped cDNAs and clones isolated from human prostate, lymph node, pituitary, mammary gland, and kidney cDNA library (Edge Biosystems, Gaithersburg, MD). The present invention encompasses the nucleotides presented in the Sequence Listing, host cells expressing such nucleotides, the expression products of such nucleotides, and: (a) nucleotides that encode mammalian homologs of the described sequences, including the specifically described NHPs, and the NHP products; (b) nucleotides that encode one or more portions of a NHP that correspond to functional domains of the NHP, and the polypeptide products specified by such nucleotide sequences, including but not limited to the novel regions of any active domain(s); (c) isolated nucleotides that encode mutant versions, engineered or naturally occurring, of a described NHP in which all or a part of at least one domain is deleted or altered, and the polypeptide products specified by such nucleotide sequences, including but not limited to soluble proteins and peptides in which all or a portion of the signal sequence is deleted; (d) nucleotides that encode chimeric fusion proteins containing all or a portion of a coding region of a NHP, or one of its domains (*e.g.*, a receptor or ligand binding domain, accessory protein/self-association domain, etc.) fused to another peptide or polypeptide; or (e) therapeutic or diagnostic derivatives of the

described polynucleotides such as oligonucleotides, antisense polynucleotides, ribozymes, dsRNA, or gene therapy constructs comprising a sequence first disclosed in the Sequence Listing.

As discussed above, the present invention includes: (a) the human DNA sequences presented in the Sequence Listing (and vectors comprising the same) and additionally contemplates any nucleotide sequence encoding a contiguous NHP open reading frame (ORF), or a contiguous exon splice junction first described in the Sequence Listing, that hybridizes to a complement of a DNA sequence presented in the Sequence Listing under highly stringent conditions, *e.g.*, hybridization to filter-bound DNA in 0.5 M $NaHPO_4$, 7% sodium dodecyl sulfate (SDS), 1 mM EDTA at 65°C, and washing in 0.1xSSC/0.1% SDS at 68°C (Ausubel F.M. *et al.*, eds., 1989, Current Protocols in Molecular Biology, Vol. I, Green Publishing Associates, Inc., and John Wiley & sons, Inc., New York, at p. 2.10.3) and encodes a functionally equivalent gene product. Additionally contemplated are any nucleotide sequences that hybridize to the complement of the DNA sequence that encode and express an amino acid sequence presented in the Sequence Listing under moderately stringent conditions, *e.g.*, washing in 0.2xSSC/0.1% SDS at 42°C (Ausubel et al., 1989, *supra*), yet still encode a functionally equivalent NHP product. Functional equivalents of a NHP include naturally occurring NHPs present in other species and mutant NHPs whether naturally occurring or engineered (by site directed mutagenesis, gene shuffling, directed evolution as described in, for example, U.S. Patent No. 5,837,458). The invention also includes degenerate nucleic acid variants of the disclosed NHP polynucleotide sequences.

Additionally contemplated are polynucleotides encoding a NHP ORF, or its functional equivalent, encoded by a polynucleotide sequence that is about 99, 95, 90, or about 85 percent similar or identical to corresponding regions of the nucleotide sequences of the Sequence Listing (as measured by BLAST sequence comparison

analysis using, for example, the GCG sequence analysis package using standard default settings).

The invention also includes nucleic acid molecules, preferably DNA molecules, that hybridize to, and are therefore the complements of, the described NHP nucleotide sequences. Such hybridization conditions may be highly stringent or less highly stringent, as described above. In instances where the nucleic acid molecules are deoxyoligonucleotides ("DNA oligos"), such molecules are generally about 16 to about 100 bases long, or about 20 to about 80, or about 34 to about 45 bases long, or any variation or combination of sizes represented therein that incorporate a contiguous region of sequence first disclosed in the Sequence Listing. Such oligonucleotides can be used in conjunction with the polymerase chain reaction (PCR) to screen libraries, isolate clones, and prepare cloning and sequencing templates, etc.

Alternatively, such NHP oligonucleotides can be used as hybridization probes for screening libraries, and assessing gene expression patterns (particularly using a micro array or high-throughput "chip" format). Additionally, a series of the described NHP oligonucleotide sequences, or the complements thereof, can be used to represent all or a portion of the described NHP sequences. An oligonucleotide or polynucleotide sequence first disclosed in at least a portion of one or more of the sequences of SEQ ID NOS: 1-15 can be used as a hybridization probe in conjunction with a solid support matrix/substrate (resins, beads, membranes, plastics, polymers, metal or metallized substrates, crystalline or polycrystalline substrates, etc.). Of particular note are spatially addressable arrays (*i.e.*, gene chips, microtiter plates, etc.) of oligonucleotides and polynucleotides, or corresponding oligopeptides and polypeptides, wherein at least one of the biopolymers present on the spatially addressable array comprises an oligonucleotide or polynucleotide

sequence first disclosed in at least one of the sequences of SEQ ID NOS: 1-15, or an amino acid sequence encoded thereby. Methods for attaching biopolymers to, or synthesizing biopolymers on, solid support matrices, and conducting binding studies thereon are disclosed in, *inter alia*, U.S. Patent Nos. 5,700,637, 5,556,752, 5,744,305, 4,631,211, 5,445,934, 5,252,743, 4,713,326, 5,424,186, and 4,689,405 the disclosures of which are herein incorporated by reference in their entirety.

Addressable arrays comprising sequences first disclosed in SEQ ID NOS:1-15 can be used to identify and characterize the temporal and tissue specific expression of a gene. These addressable arrays incorporate oligonucleotide sequences of sufficient length to confer the required specificity, yet be within the limitations of the production technology. The length of these probes is within a range of between about 8 to about 2000 nucleotides. Preferably the probes consist of 60 nucleotides and more preferably 25 nucleotides from the sequences first disclosed in SEQ ID NOS:1-15.

For example, a series of the described oligonucleotide sequences, or the complements thereof, can be used in chip format to represent all or a portion of the described sequences. The oligonucleotides, typically between about 16 to about 40 (or any whole number within the stated range) nucleotides in length can partially overlap each other and/or the sequence may be represented using oligonucleotides that do not overlap. Accordingly, the described polynucleotide sequences shall typically comprise at least about two or three distinct oligonucleotide sequences of at least about 8 nucleotides in length that are each first disclosed in the described Sequence Listing. Such oligonucleotide sequences can begin at any nucleotide present within a sequence in the Sequence Listing and proceed in either a sense (5'-to-3') orientation vis-a-vis the described sequence or in an antisense orientation.

Microarray-based analysis allows the discovery of broad patterns of genetic activity, providing new understanding of gene functions and generating novel and unexpected insight into transcriptional processes and biological mechanisms. The use of addressable arrays comprising sequences first disclosed in SEQ ID NOS:1-15 provides detailed information about transcriptional changes involved in a specific pathway, potentially leading to the identification of novel components or gene functions that manifest themselves as novel phenotypes.

Probes consisting of sequences first disclosed in SEQ ID NOS:1-15 can also be used in the identification, selection and validation of novel molecular targets for drug discovery. The use of these unique sequences permits the direct confirmation of drug targets and recognition of drug dependent changes in gene expression that are modulated through pathways distinct from the drugs intended target. These unique sequences therefore also have utility in defining and monitoring both drug action and toxicity.

As an example of utility, the sequences first disclosed in SEQ ID NOS:1-15 can be utilized in microarrays or other assay formats, to screen collections of genetic material from patients who have a particular medical condition. These investigations can also be carried out using the sequences first disclosed in SEQ ID NOS:1-15 *in silico* and by comparing previously collected genetic databases and the disclosed sequences using computer software known to those in the art.

Thus the sequences first disclosed in SEQ ID NOS:1-15 can be used to identify mutations associated with a particular disease and also as a diagnostic or prognostic assay.

Although the presently described sequences have been specifically described using nucleotide sequence, it should be appreciated that each of the sequences can uniquely be described using any of a wide variety of additional structural attributes, or combinations thereof. For example, a given sequence can be

described by the net composition of the nucleotides present within a given region of the sequence in conjunction with the presence of one or more specific oligonucleotide sequence(s) first disclosed in the SEQ ID NOS: 1-15. Alternatively, a restriction map specifying the relative positions of restriction endonuclease digestion sites, or various palindromic or other specific oligonucleotide sequences can be used to structurally describe a given sequence. Such restriction maps, which are typically generated by widely available computer programs (*e.g.*, the University of Wisconsin GCG sequence analysis package, SEQUENCHER 3.0, Gene Codes Corp., Ann Arbor, MI, etc.), can optionally be used in conjunction with one or more discrete nucleotide sequence(s) present in the sequence that can be described by the relative position of the sequence relatve to one or more additional sequence(s) or one or more restriction sites present in the disclosed sequence.

For oligonucleotide probes, highly stringent conditions may refer, for example, to washing in 6xSSC/0.05% sodium pyrophosphate at 37°C (for 14-base oligos), 48°C (for 17-base oligos), 55°C (for 20-base oligos), and 60°C (for 23-base oligos). These nucleic acid molecules may encode or act as NHP gene antisense molecules, useful, for example, in NHP gene regulation (for and/or as antisense primers in amplification reactions of NHP nucleic acid sequences). With respect to NHP gene regulation, such techniques can be used to regulate biological functions. Further, such sequences may be used as part of ribozyme and/or triple helix sequences that are also useful for NHP gene regulation.

Inhibitory antisense or double stranded oligonucleotides can additionally comprise at least one modified base moiety which is selected from the group including but not limited to 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine,

5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

The antisense oligonucleotide can also comprise at least one modified sugar moiety selected from the group including but not limited to arabinose, 2-fluoroarabinose, xylulose, and hexose.

In yet another embodiment, the antisense oligonucleotide will comprise at least one modified phosphate backbone selected from the group consisting of a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or analog thereof.

In yet another embodiment, the antisense oligonucleotide is an α-anomeric oligonucleotide. An α-anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual β-units, the strands run parallel to each other (Gautier *et al.*, 1987, Nucl. Acids Res. *15*:6625-6641). The oligonucleotide is a 2'-0-methylribonucleotide (Inoue *et al.*, 1987, Nucl. Acids Res. *15*:6131-6148), or a chimeric RNA-DNA analogue (Inoue *et al.*, 1987, FEBS Lett. *215*:327-330). Alternatively, double stranded RNA can be used to disrupt the expression and function of a targeted NHP.

Oligonucleotides of the invention can be synthesized by standard methods known in the art, *e.g.* by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides can be synthesized by the method of Stein *et al.* (1988, Nucl. Acids Res. *16*:3209), and methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin *et al.*, 1988, Proc. Natl. Acad. Sci. U.S.A. *85*:7448-7451), etc.

Low stringency conditions are well known to those of skill in the art, and will vary predictably depending on the specific organisms from which the library and the labeled sequences are derived. For guidance regarding such conditions see, for example, Sambrook *et al.*, 1989, Molecular Cloning, A Laboratory Manual (and periodic updates thereof), Cold Springs Harbor Press, N.Y.; and Ausubel *et al.*, 1989, Current Protocols in Molecular Biology, Green Publishing Associates and Wiley Interscience, N.Y.

Alternatively, suitably labeled NHP nucleotide probes can be used to screen a human genomic library using appropriately stringent conditions or by PCR. The identification and characterization of human genomic clones is helpful for identifying polymorphisms (including, but not limited to, nucleotide repeats, microsatellite alleles, single nucleotide polymorphisms, or coding single nucleotide polymorphisms), determining the genomic structure of a given locus/allele, and designing diagnostic tests. For example, sequences derived from regions adjacent to the intron/exon boundaries of the human gene can be used to design primers for use in amplification assays to detect mutations within the exons, introns, splice sites (*e.g.*, splice acceptor and/or donor sites), etc., that can be used in diagnostics and pharmacogenomics.

Further, a NHP homolog can be isolated from nucleic acid from an organism of interest by performing PCR using two degenerate or

"wobble" oligonucleotide primer pools designed on the basis of amino acid sequences within the NHP products disclosed herein. The template for the reaction may be total RNA, mRNA, and/or cDNA obtained by reverse transcription of mRNA prepared from human or non-human cell lines or tissue known or suspected to express an allele of a NHP gene.

The PCR product can be subcloned and sequenced to ensure that the amplified sequences represent the sequence of the desired NHP sequence. The PCR fragment can then be used to isolate a full length cDNA clone by a variety of methods. For example, the amplified fragment can be labeled and used to screen a cDNA library, such as a bacteriophage cDNA library. Alternatively, the labeled fragment can be used to isolate genomic clones via the screening of a genomic library.

PCR technology can also be used to isolate full length cDNA sequences. For example, RNA can be isolated, following standard procedures, from an appropriate cellular or tissue source (*i.e.*, one known, or suspected, to express a NHP sequence, such as, for example, testis tissue). A reverse transcription (RT) reaction can be performed on the RNA using an oligonucleotide primer specific for the most 5' end of the amplified fragment for the priming of first strand synthesis. The resulting RNA/DNA hybrid may then be "tailed" using a standard terminal transferase reaction, the hybrid may be digested with RNase H, and second strand synthesis may then be primed with a complementary primer. Thus, cDNA sequences upstream of the amplified fragment can be isolated. For a review of cloning strategies that can be used, see *e.g.*, Sambrook *et al.*, 1989, *supra*.

A cDNA encoding a mutant NHP sequence can be isolated, for example, by using PCR. In this case, the first cDNA strand may be synthesized by hybridizing an oligo-dT oligonucleotide to mRNA isolated from tissue known or suspected to be expressed in an individual putatively carrying a mutant NHP allele, and by

extending the new strand with reverse transcriptase. The second strand of the cDNA is then synthesized using an oligonucleotide that hybridizes specifically to the 5' end of the normal gene. Using these two primers, the product is then amplified via PCR, optionally cloned into a suitable vector, and subjected to DNA sequence analysis through methods well known to those of skill in the art. By comparing the DNA sequence of the mutant NHP allele to that of a corresponding normal NHP allele, the mutation(s) responsible for the loss or alteration of function of the mutant NHP gene product can be ascertained.

Alternatively, a genomic library can be constructed using DNA obtained from an individual suspected of or known to carry a mutant NHP allele (*e.g.*, a person manifesting a NHP-associated phenotype such as, for example, obesity, high blood pressure, connective tissue disorders, infertility, etc.), or a cDNA library can be constructed using RNA from a tissue known, or suspected, to express a mutant NHP allele. A normal NHP sequence, or any suitable fragment thereof, can then be labeled and used as a probe to identify the corresponding mutant NHP allele in such libraries. Clones containing mutant NHP sequences can then be purified and subjected to sequence analysis according to methods well known to those skilled in the art.

Additionally, an expression library can be constructed utilizing cDNA synthesized from, for example, RNA isolated from a tissue known, or suspected, to express a mutant NHP allele in an individual suspected of or known to carry such a mutant allele. In this manner, gene products made by the putatively mutant tissue can be expressed and screened using standard antibody screening techniques in conjunction with antibodies raised against normal NHP product, as described below. (For screening techniques, see, for example, Harlow, E. and Lane, eds., 1988, "Antibodies: A Laboratory Manual", Cold Spring Harbor Press, Cold Spring Harbor.)

Additionally, screening can be accomplished by screening with labeled NHP fusion proteins, such as, for example, alkaline phosphatase-NHP or NHP-alkaline phosphatase fusion proteins. In cases where a NHP mutation results in an expressed gene product with altered function (*e.g.*, as a result of a missense or a frameshift mutation), polyclonal antibodies to NHP are likely to cross-react with a corresponding mutant NHP gene product. Library clones detected via their reaction with such labeled antibodies can be purified and subjected to sequence analysis according to methods well known in the art.

The invention also encompasses (a) DNA vectors that contain any of the foregoing NHP coding sequences and/or their complements (*i.e.*, antisense); (b) DNA expression vectors that contain any of the foregoing NHP coding sequences operatively associated with a regulatory element that directs the expression of the coding sequences (for example, baculo virus as described in U.S. Patent No. 5,869,336 herein incorporated by reference); (c) genetically engineered host cells that contain any of the foregoing NHP coding sequences operatively associated with a regulatory element that directs the expression of the coding sequences in the host cell; and (d) genetically engineered host cells that express an endogenous NHP sequence under the control of an exogenously introduced regulatory element (*i.e.*, gene activation). As used herein, regulatory elements include, but are not limited to, inducible and non-inducible promoters, enhancers, operators and other elements known to those skilled in the art that drive and regulate expression. Such regulatory elements include but are not limited to the cytomegalovirus (hCMV) immediate early gene, regulatable, viral elements (particularly retroviral LTR promoters), the early or late promoters of SV40 adenovirus, the *lac* system, the *trp* system, the *TAC* system, the *TRC* system, the major operator and promoter regions of phage lambda, the control regions of fd coat protein, the promoter for 3-phosphoglycerate

kinase (PGK), the promoters of acid phosphatase, and the promoters of the yeast α-mating factors.

The present invention also encompasses antibodies and anti-idiotypic antibodies (including Fab fragments), antagonists and agonists of a NHP, as well as compounds or nucleotide constructs that inhibit expression of a NHP gene (transcription factor inhibitors, antisense and ribozyme molecules, or gene or regulatory sequence replacement constructs), or promote the expression of a NHP (*e.g.*, expression constructs in which NHP coding sequences are operatively associated with expression control elements such as promoters, promoter/enhancers, etc.).

The NHPs or NHP peptides, NHP fusion proteins, NHP nucleotide sequences, antibodies, antagonists and agonists can be useful for the detection of mutant NHPs or inappropriately expressed NHPs for the diagnosis of disease. The NHP proteins or peptides, NHP fusion proteins, NHP nucleotide sequences, host cell expression systems, antibodies, antagonists, agonists and genetically engineered cells and animals can be used for screening for drugs (or high throughput screening of combinatorial libraries) effective in the treatment of the symptomatic or phenotypic manifestations of perturbing the normal function of a NHP in the body. The use of engineered host cells and/or animals may offer an advantage in that such systems allow not only for the identification of compounds that bind to the endogenous receptor for a NHP, but can also identify compounds that trigger NHP-mediated activities or pathways.

Finally, the NHP products can be used as therapeutics. For example, soluble derivatives such as NHP peptides/domains corresponding to NHP, NHP fusion protein products (especially NHP-Ig fusion proteins, *i.e.*, fusions of a NHP, or a domain of a NHP, to an IgFc), NHP antibodies and anti-idiotypic antibodies (including Fab fragments), antagonists or agonists (including compounds that modulate or act on downstream targets in a NHP-

mediated pathway) can be used to directly treat diseases or disorders. For instance, the administration of an effective amount of soluble NHP, or a NHP-IgFc fusion protein or an anti-idiotypic antibody (or its Fab) that mimics the NHP could activate or effectively antagonize the endogenous NHP receptor. Nucleotide constructs encoding such NHP products can be used to genetically engineer host cells to express such products *in vivo*; these genetically engineered cells function as "bioreactors" in the body delivering a continuous supply of a NHP, a NHP peptide, or a NHP fusion protein to the body. Nucleotide constructs encoding functional NHP, mutant NHPs, as well as antisense and ribozyme molecules can also be used in "gene therapy" approaches for the modulation of NHP expression. Thus, the invention also encompasses pharmaceutical formulations and methods for treating biological disorders.

Various aspects of the invention are described in greater detail in the subsections below.

5.1 THE NHP SEQUENCES

The cDNA sequences and the corresponding deduced amino acid sequences of the described NHP are presented in the Sequence Listing. SEQ ID NOS:15 describes the NHP ORFs as well as flanking regions. The NHP nucleotides were obtained from human cDNA libraries using probes and/or primers generated from human gene trapped sequence tags. Expression analysis has provided evidence that the described NHP can be expressed in a variety of human cells as well as gene trapped human cells.

5.2 NHP AND NHP POLYPEPTIDES

NHPs, polypeptides, peptide fragments, mutated, truncated, or deleted forms of the NHPs, and/or NHP fusion proteins can be prepared for a variety of uses. These uses include, but are not limited to, the generation of antibodies, as reagents in

diagnostic assays, for the identification of other cellular gene products related to a NHP, as reagents in assays for screening for compounds that can be as pharmaceutical reagents useful in the therapeutic treatment of mental, biological, or medical disorders and disease.

The Sequence Listing discloses the amino acid sequence encoded by the described NHP polynucleotides. The NHPs display initiator methionines in DNA sequence contexts consistent with translation initiation sites, and apparently display signal sequences which can indicate that the described NHP ORFs are secreted proteins or possibly membrane associated.

The NHP amino acid sequences of the invention include the amino acid sequences presented in the Sequence Listing as well as analogues and derivatives thereof, as well as any oligopeptide sequence of at least about 10-40, generally about 12-35, or about 16-30 amino acids in length first disclosed in the Sequence Listing. Further, corresponding NHP homologues from other species are encompassed by the invention. In fact, any NHP encoded by the NHP nucleotide sequences described above are within the scope of the invention, as are any novel polynucleotide sequences encoding all or any novel portion of an amino acid sequence presented in the Sequence Listing. The degenerate nature of the genetic code is well known, and, accordingly, each amino acid presented in the Sequence Listing, is generically representative of the well known nucleic acid "triplet" codon, or in many cases codons, that can encode the amino acid. As such, as contemplated herein, the amino acid sequences presented in the Sequence Listing, when taken together with the genetic code (see, for example, Table 4-1 at page 109 of "Molecular Cell Biology", 1986, J. Darnell *et al.* eds., Scientific American Books, New York, NY, herein incorporated by reference) are generically representative of all the various permutations and combinations of nucleic acid sequences that can encode such amino acid sequences.

The invention also encompasses proteins that are functionally equivalent to the NHPs encoded by the presently described nucleotide sequences as judged by any of a number of criteria, including, but not limited to, the ability to bind and cleave a substrate of a NHP, or the ability to effect an identical or complementary downstream pathway, or a change in cellular metabolism (*e.g.*, proteolytic activity, ion flux, tyrosine phosphorylation, etc.). Such functionally equivalent NHP proteins include, but are not limited to, additions or substitutions of amino acid residues within the amino acid sequence encoded by the NHP nucleotide sequences described above, but which result in a silent change, thus producing a functionally equivalent gene product. Amino acid substitutions can be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues involved. For example, nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan, and methionine; polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine, and glutamine; positively charged (basic) amino acids include arginine, lysine, and histidine; and negatively charged (acidic) amino acids include aspartic acid and glutamic acid.

A variety of host-expression vector systems can be used to express the NHP nucleotide sequences of the invention. Where, as in the present instance, the NHP products or NHP polypeptides can be produced in soluble or secreted forms (by removing one or more transmembrane domains where applicable), the peptide or polypeptide can be recovered from the culture media. Such expression systems also encompass engineered host cells that express a NHP, or a functional equivalent, *in situ*. Purification or enrichment of NHP from such expression systems can be accomplished using appropriate detergents and lipid micelles and methods well known to those skilled in the art. However, such

engineered host cells themselves may be used in situations where it is important not only to retain the structural and functional characteristics of the NHP, but to assess biological activity, *e.g.*, in drug screening assays.

The expression systems that may be used for purposes of the invention include but are not limited to microorganisms such as bacteria (*e.g.*, *E. coli*, *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing NHP nucleotide sequences; yeast (*e.g.*, *Saccharomyces*, *Pichia*) transformed with recombinant yeast expression vectors containing NHP encoding nucleotide sequences; insect cell systems infected with recombinant virus expression vectors (*e.g.*, baculovirus) containing NHP sequences; plant cell systems infected with recombinant virus expression vectors (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (*e.g.*, Ti plasmid) containing NHP nucleotide sequences; or mammalian cell systems (*e.g.*, COS, CHO, BHK, 293, 3T3) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (*e.g.*, metallothionein promoter) or from mammalian viruses (*e.g.*, the adenovirus late promoter; the vaccinia virus 7.5K promoter).

In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the NHP product being expressed. For example, when a large quantity of such a protein is to be produced for the generation of pharmaceutical compositions of or containing NHP, or for raising antibodies to a NHP, vectors that direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the *E. coli* expression vector pUR278 (Ruther *et al.*, 1983, EMBO J. *2*:1791), in which a NHP coding sequence may be ligated

individually into the vector in frame with the *lacZ* coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, 1985, Nucleic Acids Res. *13*:3101-3109; Van Heeke & Schuster, 1989, J. Biol. Chem. *264*:5503-5509); and the like. pGEX vectors (Pharmacia or American Type Culture Collection) can also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption to glutathione-agarose beads followed by elution in the presence of free glutathione. The PGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

In an insect system, *Autographa californica* nuclear polyhidrosis virus (AcNPV) is used as a vector to express foreign sequences. The virus grows in *Spodoptera frugiperda* cells. A NHP coding sequence can be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter). Successful insertion of NHP coding sequence will result in inactivation of the polyhedrin gene and production of non-occluded recombinant virus (*i.e.*, virus lacking the proteinaceous coat coded for by the polyhedrin gene). These recombinant viruses are then used to infect Spodoptera frugiperda cells in which the inserted sequence is expressed (*e.g.*, see Smith *et al.*, 1983, J. Virol. 46: 584; Smith, U.S. Patent No. 4,215,051).

In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the NHP nucleotide sequence of interest may be ligated to an adenovirus transcription/translation control complex, *e.g.*, the late promoter and tripartite leader sequence. This chimeric sequence may then be inserted in the adenovirus genome by *in vitro* or *in vivo* recombination. Insertion in a non-

essential region of the viral genome (*e.g.*, region E1 or E3) will result in a recombinant virus that is viable and capable of expressing a NHP product in infected hosts (*e.g.*, See Logan & Shenk, 1984, Proc. Natl. Acad. Sci. USA *81*:3655-3659). Specific initiation signals may also be required for efficient translation of inserted NHP nucleotide sequences. These signals include the ATG initiation codon and adjacent sequences. In cases where an entire NHP sequence or cDNA, including its own initiation codon and adjacent sequences, is inserted into the appropriate expression vector, no additional translational control signals may be needed. However, in cases where only a portion of a NHP coding sequence is inserted, exogenous translational control signals, including, perhaps, the ATG initiation codon, must be provided. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (See Bittner *et al.*, 1987, Methods in Enzymol. *153*:516-544).

In addition, a host cell strain may be chosen that modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (*e.g.*, glycosylation) and processing (*e.g.*, cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript,

glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include, but are not limited to, CHO, VERO, BHK, HeLa, COS, MDCK, 293, 3T3, WI38, and in particular, human cell lines.

For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the NHP sequences described above can be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (*e.g.*, promoter, enhancer sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the NHP product. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that affect the endogenous activity of the NHP product.

A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler, *et al.*, 1977, Cell *11*:223), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, 1962, Proc. Natl. Acad. Sci. USA *48*:2026), and adenine phosphoribosyltransferase (Lowy, *et al.*, 1980, Cell *22*:817) genes can be employed in tk^-, $hgprt^-$ or $aprt^-$ cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler, *et al.*, 1980, Natl. Acad. Sci. USA 77:3567; O'Hare, *et al.*, 1981, Proc. Natl. Acad. Sci. USA *78*:1527); gpt,

which confers resistance to mycophenolic acid (Mulligan & Berg, 1981, Proc. Natl. Acad. Sci. USA *78*:2072); neo, which confers resistance to the aminoglycoside G-418 (Colberre-Garapin, *et al.*, 1981, J. Mol. Biol. *150*:1); and hygro, which confers resistance to hygromycin (Santerre, *et al.*, 1984, Gene *30*:147).

Alternatively, any fusion protein can be readily purified by utilizing an antibody specific for the fusion protein being expressed. For example, a system described by Janknecht *et al.* allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht, *et al.*, 1991, Proc. Natl. Acad. Sci. USA *88*:8972-8976). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the gene's open reading frame is translationally fused to an amino-terminal tag consisting of six histidine residues. Extracts from cells infected with recombinant vaccinia virus are loaded onto Ni^{2+}·nitriloacetic acid-agarose columns and histidine-tagged proteins are selectively eluted with imidazole-containing buffers.

Also encompassed by the present invention are fusion proteins that direct the NHP to a target organ and/or facilitate transport across the membrane into the cytosol. Conjugation of NHPs to antibody molecules or their Fab fragments could be used to target cells bearing a particular epitope. Attaching the appropriate signal sequence to the NHP would also transport the NHP to the desired location within the cell. Alternatively targeting of NHP or its nucleic acid sequence might be achieved using liposome or lipid complex based delivery systems. Such technologies are described in Liposomes:A Practical Approach, New,RRC ed., Oxford University Press, New York and in U.S. Patents Nos. 4,594,595, 5,459,127, 5,948,767 and 6,110,490 and their respective disclosures which are herein incorporated by reference in their entirety. Additionally embodied are novel protein constructs engineered in such a way that they facilitate transport of the NHP to the target site or desired organ, where they cross the cell

membrane and/or the nucleus where the NHP can exert its functional activity. This goal may be achieved by coupling of the NHP to a cytokine or other ligand that provides targeting specificity, and/or to a protein transducing domain (see generally U.S. applications Ser. No. 60/111,701 and 60/056,713, both of which are herein incorporated by reference, for examples of such transducing sequences) to facilitate passage across cellular membranes and can optionally be engineered to include nuclear localization sequences.

5.3 ANTIBODIES TO NHP PRODUCTS

Antibodies that specifically recognize one or more epitopes of a NHP, or epitopes of conserved variants of a NHP, or peptide fragments of a NHP are also encompassed by the invention. Such antibodies include but are not limited to polyclonal antibodies, monoclonal antibodies (mAbs), humanized or chimeric antibodies, single chain antibodies, Fab fragments, $F(ab')_2$ fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments of any of the above.

The antibodies of the invention may be used, for example, in the detection of NHP in a biological sample and may, therefore, be utilized as part of a diagnostic or prognostic technique whereby patients may be tested for abnormal amounts of NHP. Such antibodies may also be utilized in conjunction with, for example, compound screening schemes for the evaluation of the effect of test compounds on expression and/or activity of a NHP gene product. Additionally, such antibodies can be used in conjunction gene therapy to, for example, evaluate the normal and/or engineered NHP-expressing cells prior to their introduction into the patient. Such antibodies may additionally be used as a method for the inhibition of abnormal NHP activity. Thus, such antibodies may, therefore, be utilized as part of treatment methods.

For the production of antibodies, various host animals may be immunized by injection with the NHP, an NHP peptide (*e.g.*, one corresponding to a functional domain of an NHP), truncated NHP polypeptides (NHP in which one or more domains have been deleted), functional equivalents of the NHP or mutated variant of the NHP. Such host animals may include but are not limited to pigs, rabbits, mice, goats, and rats, to name but a few. Various adjuvants may be used to increase the immunological response, depending on the host species, including but not limited to Freund's adjuvant (complete and incomplete), mineral salts such as aluminum hydroxide or aluminum phosphate, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and *Corynebacterium parvum*. Alternatively, the immune response could be enhanced by combination and or coupling with molecules such as keyhole limpet hemocyanin, tetanus toxoid, diptheria toxoid, ovalbumin, cholera toxin or fragments thereof. Polyclonal antibodies are heterogeneous populations of antibody molecules derived from the sera of the immunized animals.

Monoclonal antibodies, which are homogeneous populations of antibodies to a particular antigen, can be obtained by any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique of Kohler and Milstein, (1975, Nature *256*:495-497; and U.S. Patent No. 4,376,110), the human B-cell hybridoma technique (Kosbor *et al.*, 1983, Immunology Today *4*:72; Cole *et al.*, 1983, Proc. Natl. Acad. Sci. USA *80*:2026-2030), and the EBV-hybridoma technique (Cole *et al.*, 1985, Monoclonal Antibodies And Cancer Therapy, Alan R. Liss, Inc., pp. 77-96). Such antibodies may be of any immunoglobulin class including IgG, IgM, IgE, IgA, IgD and any subclass thereof. The hybridoma producing the mAb of this invention may be cultivated *in vitro* or

in vivo. Production of high titers of mAbs in vivo makes this the presently preferred method of production.

In addition, techniques developed for the production of "chimeric antibodies" (Morrison *et al.*, 1984, Proc. Natl. Acad. Sci., *81*:6851-6855; Neuberger *et al.*, 1984, Nature, *312*:604-608; Takeda *et al.*, 1985, Nature, *314*:452-454) by splicing the genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used. A chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region. Such technologies are described in U.S. Patents Nos. 6,075,181 and 5,877,397 and their respective disclosures which are herein incorporated by reference in their entirety. Also favored is the production of fully humanized monoclonal antibodies as described in US Patent No. 6,150,584 and respective disclosures which are herein incorporated by reference in their entirety.

Alternatively, techniques described for the production of single chain antibodies (U.S. Patent 4,946,778; Bird, 1988, Science *242*:423-426; Huston *et al.*, 1988, Proc. Natl. Acad. Sci. USA *85*:5879-5883; and Ward *et al.*, 1989, Nature *334*:544-546) can be adapted to produce single chain antibodies against NHP gene products. Single chain antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide.

Antibody fragments which recognize specific epitopes may be generated by known techniques. For example, such fragments include, but are not limited to: the $F(ab')_2$ fragments which can be produced by pepsin digestion of the antibody molecule and the Fab fragments which can be generated by reducing the disulfide bridges of the $F(ab')_2$ fragments. Alternatively, Fab expression libraries may be constructed (Huse *et al.*, 1989, Science,

246:1275-1281) to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity.

Antibodies to a NHP can, in turn, be utilized to generate anti-idiotype antibodies that "mimic" a given NHP, using techniques well known to those skilled in the art. (See, *e.g.*, Greenspan & Bona, 1993, FASEB J *7(5)*:437-444; and Nissinoff, 1991, J. Immunol. *147(8)*:2429-2438). For example antibodies which bind to a NHP domain and competitively inhibit the binding of NHP to its cognate receptor can be used to generate anti-idiotypes that "mimic" the NHP and, therefore, bind and activate or neutralize a receptor. Such anti-idiotypic antibodies or Fab fragments of such anti-idiotypes can be used in therapeutic regimens involving a NHP signaling pathway.

The present invention is not to be limited in scope by the specific embodiments described herein, which are intended as single illustrations of individual aspects of the invention, and functionally equivalent methods and components are within the scope of the invention. Indeed, various modifications of the invention, in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the appended claims. All cited publications, patents, and patent applications are herein incorporated by reference in their entirety.

WHAT IS CLAIMED IS:

1. An isolated nucleic acid molecule comprising at least 24 contiguous bases of nucleotide sequence first disclosed in SEQ ID NO: 1.

2. An isolated nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the amino acid sequence shown in SEQ ID NO: 2; and

(b) hybridizes under stringent conditions to the nucleotide sequence of SEQ ID NO: 1 or the complement thereof.

3. An isolated nucleic acid molecule encoding the amino acid sequence described in SEQ ID NO: 2.

4. An isolated oligopeptide comprising at least about 12 amino acids in a sequence first disclosed in SEQ ID NO:2.

ABSTRACT

Novel human polynucleotide and polypeptide sequences are disclosed that can be used in therapeutic, diagnostic, and pharmacogenomic applications.

PCT POWER OF ATTORNEY

LEX-0118-PCT

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0-1	PCT Power of Attorney (for an international application filed under the Patent Cooperation Treaty) (PCT Rule 90.4)	
0-1-1	Prepared using	PCT-EASY Version 2.91 (updated 01.01.2001)

1	The undersigned applicant(s)	LEXICON GENETICS INCORPORATED
1-1-1	hereby appoints (appoint) the following person	ISHIMOTO, Lance, K.; SEFERIAN, Peter, G. LEXICON GENETICS INCORPORATED 4000 Research Forest Drive The Woodlands, TX 77381 United States of America
1-2	as	agent
1-3	to represent the undersigned before	all the competent International Authorities
1-4	in connection with the international application identified below:	
1-4-1	Title of the invention	NOVEL HUMAN ENZYMES AND POLYNUCLEOTIDES ENCODING THE SAME
1-4-2	Applicant's or agent's file reference	LEX-0118-PCT
1-4-3	International application number (if already available)	
1-4-4	filed with the following Office as receiving Office	United States Patent and Trademark Office (USPTO) (RO/US)
1-5	and to make or receive payments on behalf of the undersigned.	

2-1	Signature of applicant	
2-1-1	Name	LEXICON GENETICS INCORPORATED
2-1-2	Name of signatory	Lance K. Ishimoto Reg No. 41,526
2-1-3	Capacity	VP - Intellectual Property
3	Date	25 January 2001 (25.01.2001)

IN THE PATENT COOPERATION TREATY

Applicant: LEXICON GENETICS INCORPORATED

Int'l. Appl. No.: to be assigned Attorney Docket No.: LEX-0118-PCT

Int'l. Filing Date: January 25, 2001

For: NOVEL HUMAN ENZYMES AND POLYNUCLEOTIDES ENCODING THE SAME

VERIFIED STATEMENT

BOX PCT
Asst. Commission for Patents
Washington, D.C. 20231

Attn: RO/US
Sir:

I, DRENDA D. THOMAS, do declare and state as follows:

1. I prepared a Sequence Listing in paper and computer readable form in connection with the above-captioned patent application, both of which are being submitted herewith.

2. I hereby state that the contents of the paper and computer readable copies of the Sequence Listing are the same.

Signed

1/25/01
Date

Drenda Thomas
Drenda D. Thomas

SEQUENCE LISTING

<110> LEXICON GENETICS INCORPORATED

<120> Novel Human Enzymes and Polynucleotides
Encoding the Same

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<213> Homo sapiens

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35 40 45
Tyr Gly Ala Lys Tyr Phe Pro Glu Tyr Ala Glu Lys Ile Pro Gly Glu
50 55 60
Ser Thr Gln Lys Leu Ser Glu Val Ala Lys Glu Cys Ser Ile Tyr Leu
65 70 75 80
Ile Gly Gly Ser Ile Pro Glu Glu Asp Ala Gly Lys Leu Tyr Asn Thr
85 90 95

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Cys Ala Val Phe Gly Pro Asp Gly Thr Leu Leu Ala Lys Tyr Arg Lys
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Ile His Leu Phe Asp Ile Asp Val Pro Gly Lys Ile Thr Phe Gln Glu
        115                 120                 125
Ser Lys Thr Leu Ser Pro Gly Asp Ser Phe Ser Thr Phe Asp Thr Pro
    130                 135                 140
Tyr Cys Arg Val Gly Leu Gly Ile Cys Tyr Asp Met Arg Phe Ala Glu
145                 150                 155                 160
Leu Ala Gln Ile Tyr Ala Gln Arg Gly Cys Gln Leu Leu Val Tyr Pro
                165                 170                 175
Gly Ala Phe Asn Leu Thr Thr Gly Pro Ala His Trp Glu Leu Leu Gln
            180                 185                 190
Arg Ser Arg Ala Val Asp Asn Gln Val Tyr Val Ala Thr Ala Ser Pro
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Ala Arg Asp Asp Lys Ala Ser Tyr Val Ala Trp Gly His Ser Thr Val
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Val Asn Pro Trp Gly Glu Val Leu Ala Lys Ala Gly Thr Glu Glu Ala
225                 230                 235                 240
Ile Val Tyr Ser Asp Ile Asp Leu Lys Lys Leu Ala Glu Ile Arg Gln
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<400> 3

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gcctggggac acagcaccgt ggtgaaccct tgggggggagg ttctagccaa agctggcaca     360
gaagaagcaa tcgtgtattc agacatagac ctgaagaagc tggctgaaat acgccagcaa     420
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<213> Homo sapiens

<400> 4

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Leu Gly Ile Cys Tyr Asp Met Arg Phe Ala Glu Leu Ala Gln Ile Tyr
        35                  40                  45
Ala Gln Arg Gly Cys Gln Leu Leu Val Tyr Pro Gly Ala Phe Asn Leu
    50                  55                  60
Thr Thr Gly Pro Ala His Trp Glu Leu Leu Gln Arg Ser Arg Ala Val
65                  70                  75                  80
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Asp Asn Gln Val Tyr Val Ala Thr Ala Ser Pro Ala Arg Asp Asp Lys
                85                  90                  95
Ala Ser Tyr Val Ala Trp Gly His Ser Thr Val Val Asn Pro Trp Gly
            100                 105                 110
Glu Val Leu Ala Lys Ala Gly Thr Glu Glu Ala Ile Val Tyr Ser Asp
        115                 120                 125
Ile Asp Leu Lys Lys Leu Ala Glu Ile Arg Gln Gln Ile Pro Val Phe
    130                 135                 140
Arg Gln Lys Arg Ser Asp Leu Tyr Ala Val Glu Met Lys Lys Pro
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gctgttgata atcaggtgta tgtggccaca gcctctcctg cccgggatga caaagcctcc     180
tatgttgcct ggggacacag caccgtggtg aacccttggg gggaggttct agccaaagct     240
ggcacagaag aagcaatcgt gtattcagac atagacctga agaagctggc tgaaatacgc     300
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<213> Homo sapiens

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Trp Glu Leu Leu Gln Arg Ser Arg Ala Val Asp Asn Gln Val Tyr Val
        35                  40                  45
Ala Thr Ala Ser Pro Ala Arg Asp Asp Lys Ala Ser Tyr Val Ala Trp
    50                  55                  60
Gly His Ser Thr Val Val Asn Pro Trp Gly Glu Val Leu Ala Lys Ala
65                  70                  75                  80
Gly Thr Glu Glu Ala Ile Val Tyr Ser Asp Ile Asp Leu Lys Lys Leu
                85                  90                  95
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            100                 105                 110
Leu Tyr Ala Val Glu Met Lys Lys Pro
        115                 120

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<212> DNA
<213> Homo sapiens

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<211> 168
<212> PRT
<213> Homo sapiens

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            20                  25                  30
Leu Gly Ile Cys Tyr Asp Met Arg Phe Ala Glu Leu Ala Gln Ile Tyr
        35                  40                  45
Ala Gln Arg Gly Cys Gln Leu Leu Val Tyr Pro Gly Ala Phe Asn Leu
    50                  55                  60
Thr Thr Gly Pro Ala His Trp Glu Leu Leu Gln Arg Ser Arg Ala Val
65                  70                  75                  80
Asp Asn Gln Val Tyr Val Ala Thr Ala Ser Pro Ala Arg Asp Asp Lys
                85                  90                  95
Ala Ser Tyr Val Ala Trp Gly His Ser Thr Val Val Asn Pro Trp Gly
            100                 105                 110
Glu Val Leu Ala Lys Ala Gly Thr Glu Glu Ala Ile Val Tyr Ser Asp
        115                 120                 125
Ile Asp Leu Lys Lys Leu Ala Glu Ile Arg Gln Gln Ile Pro Val Phe
    130                 135                 140
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145                 150                 155                 160
Asn Pro His Arg Ser Phe Leu Lys
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<211> 393
<212> DNA
<213> Homo sapiens

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gctgttgata atcaggtgta tgtggccaca gcctctcctg cccgggatga caaagcctcc     180
tatgttgcct ggggacacag caccgtggtg aacccttggg gggaggttct agccaaagct     240
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<212> PRT
<213> Homo sapiens
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35 40 45
Ala Thr Ala Ser Pro Ala Arg Asp Asp Lys Ala Ser Tyr Val Ala Trp
50 55 60
Gly His Ser Thr Val Val Asn Pro Trp Gly Glu Val Leu Ala Lys Ala
65 70 75 80
Gly Thr Glu Glu Ala Ile Val Tyr Ser Asp Ile Asp Leu Lys Lys Leu
85 90 95
Ala Glu Ile Arg Gln Gln Ile Pro Val Phe Arg Gln Lys Arg Asn Ile
100 105 110
Phe Leu Asn Met Gln Arg Lys Phe Leu Val Asn Pro His Arg Ser Phe
115 120 125
Leu Lys
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<211> 459
<212> DNA
<213> Homo sapiens

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attggaggct ctatccctga agaggatgct gggaaattat ataacacctg tgctgtgttt 300
gggcctgatg gaactttact agcaaagtat agaaagatcc atctgtttga cattgatgtt 360
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<211> 152
<212> PRT
<213> Homo sapiens

<400> 12
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Thr Gln Gly Ala Lys Ile Val Ser Leu Pro Glu Cys Phe Asn Ser Pro
35 40 45
Tyr Gly Ala Lys Tyr Phe Pro Glu Tyr Ala Glu Lys Ile Pro Gly Glu
50 55 60
Ser Thr Gln Lys Leu Ser Glu Val Ala Lys Glu Cys Ser Ile Tyr Leu
65 70 75 80
Ile Gly Gly Ser Ile Pro Glu Glu Asp Ala Gly Lys Leu Tyr Asn Thr
85 90 95
Cys Ala Val Phe Gly Pro Asp Gly Thr Leu Leu Ala Lys Tyr Arg Lys
100 105 110
Ile His Leu Phe Asp Ile Asp Val Pro Gly Lys Ile Thr Phe Gln Glu

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Met Tyr Gln Ile Ser Leu Pro Leu
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<213> Homo sapiens

<400> 13

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            20                  25                  30
Thr Gln Gly Ala Lys Ile Val Ser Leu Pro Glu Cys Phe Asn Ser Pro
        35                  40                  45
Tyr Gly Ala Lys Tyr Phe Pro Glu Tyr Ala Glu Lys Ile Pro Gly Glu
    50                  55                  60
Ser Thr Gln Lys Leu Ser Glu Val Ala Lys Glu Cys Ser Ile Tyr Leu
65                  70                  75                  80
Ile Gly Gly Ser Ile Pro Glu Glu Asp Ala Gly Lys Leu Tyr Asn Thr
                85                  90                  95
Cys Ala Val Phe Gly Pro Asp Gly Thr Leu Leu Ala Lys Tyr Arg Lys
            100                 105                 110
Ile His Leu Phe Asp Ile Asp Val Pro Gly Lys Ile Thr Phe Gln Glu
        115                 120                 125
Ser Lys Thr Leu Ser Pro Gly Asp Ser Phe Ser Thr Phe Asp Thr Pro
    130                 135                 140
Tyr Cys Arg Val Gly Leu Gly Ile Cys Tyr Asp Met Arg Phe Ala Glu
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Leu Ala Gln Ile Tyr Ala Gln Arg Gly Cys Gln Leu Leu Val Tyr Pro
                165                 170                 175
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Ala Arg Asp Asp Lys Ala Ser Tyr Val Ala Trp Gly His Ser Thr Val
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Val Asn Pro Trp Gly Glu Val Leu Ala Lys Ala Gly Thr Glu Glu Ala
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Ile Val Tyr Ser Asp Ile Asp Leu Lys Lys Leu Ala Glu Ile Arg Gln
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Gln Ile Pro Val Phe Arg Gln Lys Arg Asn Ile Phe Leu Asn Met Gln
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<210> 15
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<212> DNA
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PCT (ANNEX - FEE CALCULATION SHEET)

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0	**For receiving Office use only**	
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0-2	Date stamp of the receiving Office	

0-4	**Form - PCT/RO/101 (Annex) PCT Fee Calculation Sheet**				
0-4-1	Prepared using		PCT-EASY Version 2.91 (updated 01.01.2001)		
0-9	**Applicant's or agent's file reference**		LEX-0118-PCT		
2	**Applicant**		LEXICON GENETICS INCORPORATED		
12	**Calculation of prescribed fees**		fee amount/multiplier	total amounts (USD)	
12-1	Transmittal fee	T	⇨	240	
12-2	Search fee	S	⇨	846	
12-3	International fee Basic fee (first 30 sheets)	b1	382		
12-4	Remaining sheets		11		
12-5	Additional amount	(X)	9		
12-6	Total additional amount	b2	99		
12-7	b1 + b2 =	B	481		
12-8	Designation fees Number of designations contained in international application		86		
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12-10	Amount of designation fee	(X)	82		
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12-13	Total International fee (B+D-R)	I	⇨	856	
12-14	Fee for priority document Number of priority documents requested		1		
12-15	Fee per document	(X)	15		
12-16	Total priority document fee	P	⇨	15	
12-17	**TOTAL FEES PAYABLE (T+S+I+P)**		⇨	1,957	
12-19	**Mode of payment**		authorization to charge deposit account		
12-20	**Deposit account instructions** The receiving Office:		United States Patent and Trademark Office (USPTO) (RO/US)		
12-20-1	is hereby authorized to charge the total fees indicated above to my deposit account		✓		
12-20-2	is hereby authorized to charge any deficiency or credit any over-payment in the total fees indicated above to my deposit account		✓		

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12-21	Deposit account No.	50-0892
12-22	Date	25 January 2001 (25.01.2001)
12-23	Name and signature	ISHIMOTO, Lance, K.

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13-2-2	Validation messages States	Green? More designations could be made. The following States have not been designated: US. Please verify.
13-2-6	Validation messages Contents	Green? The international application contains no drawings. Please verify.
13-2-8	Validation messages Payment	Green? Please ensure that you have a valid deposit account with the receiving Office selected.

10/069169

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Box Patent Application
Express Mail No.: EL672756762US
Date Mailed 1-25-01 U.S. Appl. Ser. No.: to be assigned
Inventors: Donaho, Hilbun, Scoville, Turner, Friedrich, Abuin,
Title: Novel Human Enzymes + Zambrowicz, Sands
Polynucleotides Encoding the Same,
Attorney Docket No.: LEX-0118-USA

X Specification 28 pages total (26 pages spec; 1 claim page(s); 1 page Abstr
X Transmittal Letter (original and copy)
___ Drawings (_____ pages; _____ number of drawings)
X Sequence Listing (8 pages)
Other: return postcard; unsigned Declaration

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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53 (b))

Attorney Docket No.	LEX-0118-USA
First Inventor	Gregory Donoho *et al.*
Title	Novel Human Enzymes and Polynucleotides Encoding the Same
Express Mail label No.	EL 672 756 762 US

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO: **Assistant Commissioner for Patents, Box Patent Application, Washington, DC 20231**

1. [ ] Fee Transmittal Form (e.g., PTO/SB/17) *(Submit an original and a duplicate for fee processing)*
2. [X] Applicant claims small entity status. See 37 CFR 1.27.
3. [X] Specification *(preferred arrangement set forth below)* [Total Pages 28]
   - Descriptive title of the Invention
   - Cross Reference to Related Applications
   - Statement Regarding Fed sponsored R & D
   - Reference to sequence listing, a table, or a computer program listing appendix
   - Background of the Invention
   - Brief Summary of the Invention
   - Brief Description of the drawings *(if filed)*
   - Detailed Description
   - Claim(s)
   - Abstract of the disclosure
4. [ ] Drawing(s) *(35 U.S.C.113)* [Total Sheets]
5. Oath or Declaration [Total Pages 3]
   a. [X] unexecuted (original or copy)
   b. [ ] Copy from a prior application (37 CFR 1.63(d)) *(for continuation/divisional with Box 17 completed)*
      i. [ ] DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).
6. [ ] Application Data Sheet. See 37 CFR 1.76
7. [ ] CD-ROM or CD-R in duplicate, large table or Computer Program (*Appendix*)
8. Nucleotide and/or Amino Acid Sequence Submission *(if applicable, all necessary)*
   a. [ ] Computer Readable Form (CRF)
   b. Specification Sequence Listing on:
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ACCOMPANYING APPLICATION PARTS

9. [ ] Assignment Papers (cover sheet & document(s))
10. [ ] 37 CFR 3.73(b) Statement *(when there is an assignee)* [X] Power of Attorney
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17. If a CONTINUING APPLICATION, *check appropriate box, and supply the requisite information below and in a preliminary amendment, or in an Application Data Sheet under 37 CFR 1.76:*

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Prior application information: *Examiner* _____ *Group/Art Unit:* _____

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Name (Print/Type)	Lance K. Ishimoto	*Registration No. (Attorney/Agent)*	41866
Signature		*Date*	January 25, 2001

NOVEL HUMAN ENZYMES AND POLYNUCLEOTIDES ENCODING THE SAME

The present application claims the benefit of U.S. Provisional Application Number 60/179,000 which was filed on January 28, 2000 and is herein incorporated by reference in its entirety.

1. INTRODUCTION

The present invention relates to the discovery, identification, and characterization of novel human polynucleotides encoding proteins sharing sequence similarity with mammalian enzymes. The invention encompasses the described polynucleotides, host cell expression systems, the encoded protein, fusion proteins, polypeptides and peptides, antibodies to the encoded proteins and peptides, and sequencetically engineered animals that either lack or over express the disclosed sequences, antagonists and agonists of the proteins, and other compounds that modulate the expression or activity of the proteins encoded by the disclosed polynucleotides that can be used for diagnosis, drug screening, clinical trial monitoring and the treatment of physiological disorders.

2. BACKGROUND OF THE INVENTION

Enzymes are biological catalysts that modify biological substrates, including proteins, as part of degradation, maturation, catabolic, metabolic, differentiation, and secretory pathways within the body. Enzyme abnormalities have thus been associated with, *inter alia*, growth, development, protein and cellular senescence, cancer, or other diseases.

3. SUMMARY OF THE INVENTION

The present invention relates to the discovery, identification, and characterization of nucleotides that encode novel human proteins, and the corresponding amino acid sequences

of these proteins. The novel human proteins (NHPs) described for the first time herein share structural similarity with nitrilase proteins from a wide variety of living organisms.

The novel human nucleic acid (cDNA) sequences described herein, encode proteins/open reading frames (ORFs) of 276, 159, 121, 168, 130, 152, and 285 amino acids in length (see respectively SEQ ID NOS: 2, 4, 6, 8, 10, 12 and 14).

The invention also encompasses agonists and antagonists of the described NHPs including small molecules, large molecules, mutant NHPs, or portions thereof that compete with native NHPs, NHP peptides, and antibodies, as well as nucleotide sequences that can be used to inhibit the expression of the described NHPs (*e.g.*, antisense and ribozyme molecules, and gene or regulatory sequence replacement constructs) or to enhance the expression of the described NHPs (*e.g.*, expression constructs that place the described sequence under the control of a strong promoter system), and transgenic animals that express a NHP transgene, or "knock-outs" (which can be conditional) that do not express a functional NHP.

Further, the present invention also relates to processes for identifying compounds that modulate, *i.e.*, act as agonists or antagonists, of NHP expression and/or NHP activity that utilize purified preparations of the described NHP and/or NHP product, or cells expressing the same. Such compounds can be used as therapeutic agents for the treatment of any of a wide variety of symptoms associated with biological disorders or imbalances.

4. DESCRIPTION OF THE SEQUENCE LISTING AND FIGURES

The Sequence Listing provides the sequences of the NHP ORFs encoding the described NHP amino acid sequences. SEQ ID NOS:15 describe representative a nitrilase-like ORF with flanking sequences.

5. DETAILED DESCRIPTION OF THE INVENTION

The NHPs, described for the first time herein, are novel proteins that are expressed in, *inter alia,* human cell lines, gene trapped cells and human brain, fetal brain, pituitary, cerebellum, spinal cord, thymus, spleen, lymph node, bone marrow, trachea, lung, kidney, fetal liver, liver, prostate, testis, thyroid, adrenal gland, pancreas, salivary gland, stomach, small intestine, colon, skeletal muscle, heart, placenta, mammary gland, adipose, skin, esophagus, bladder, pericardium, hypothalamus, ovary, fetal kidney, and fetal lung cells.

The described sequences were compiled from gene trapped cDNAs and clones isolated from human prostate, lymph node, pituitary, mammary gland, and kidney cDNA library (Edge Biosystems, Gaithersburg, MD). The present invention encompasses the nucleotides presented in the Sequence Listing, host cells expressing such nucleotides, the expression products of such nucleotides, and: (a) nucleotides that encode mammalian homologs of the described sequences, including the specifically described NHPs, and the NHP products; (b) nucleotides that encode one or more portions of a NHP that correspond to functional domains of the NHP, and the polypeptide products specified by such nucleotide sequences, including but not limited to the novel regions of any active domain(s); (c) isolated nucleotides that encode mutant versions, engineered or naturally occurring, of a described NHP in which all or a part of at least one domain is deleted or altered, and the polypeptide products specified by such nucleotide sequences, including but not limited to soluble proteins and peptides in which all or a portion of the signal sequence is deleted; (d) nucleotides that encode chimeric fusion proteins containing all or a portion of a coding region of a NHP, or one of its domains (*e.g.*, a receptor or ligand binding domain, accessory protein/self-association domain, etc.) fused to another peptide or polypeptide; or (e) therapeutic or diagnostic derivatives of the

described polynucleotides such as oligonucleotides, antisense polynucleotides, ribozymes, dsRNA, or gene therapy constructs comprising a sequence first disclosed in the Sequence Listing.

As discussed above, the present invention includes: (a) the human DNA sequences presented in the Sequence Listing (and vectors comprising the same) and additionally contemplates any nucleotide sequence encoding a contiguous NHP open reading frame (ORF), or a contiguous exon splice junction first described in the Sequence Listing, that hybridizes to a complement of a DNA sequence presented in the Sequence Listing under highly stringent conditions, *e.g.*, hybridization to filter-bound DNA in 0.5 M $NaHPO_4$, 7% sodium dodecyl sulfate (SDS), 1 mM EDTA at 65°C, and washing in 0.1xSSC/0.1% SDS at 68°C (Ausubel F.M. *et al.*, eds., 1989, Current Protocols in Molecular Biology, Vol. I, Green Publishing Associates, Inc., and John Wiley & sons, Inc., New York, at p. 2.10.3) and encodes a functionally equivalent gene product. Additionally contemplated are any nucleotide sequences that hybridize to the complement of the DNA sequence that encode and express an amino acid sequence presented in the Sequence Listing under moderately stringent conditions, *e.g.*, washing in 0.2xSSC/0.1% SDS at 42°C (Ausubel et al., 1989, *supra*), yet still encode a functionally equivalent NHP product. Functional equivalents of a NHP include naturally occurring NHPs present in other species and mutant NHPs whether naturally occurring or engineered (by site directed mutagenesis, gene shuffling, directed evolution as described in, for example, U.S. Patent No. 5,837,458). The invention also includes degenerate nucleic acid variants of the disclosed NHP polynucleotide sequences.

Additionally contemplated are polynucleotides encoding a NHP ORF, or its functional equivalent, encoded by a polynucleotide sequence that is about 99, 95, 90, or about 85 percent similar or identical to corresponding regions of the nucleotide sequences of the Sequence Listing (as measured by BLAST sequence comparison

analysis using, for example, the GCG sequence analysis package using standard default settings).

The invention also includes nucleic acid molecules, preferably DNA molecules, that hybridize to, and are therefore the complements of, the described NHP nucleotide sequences. Such hybridization conditions may be highly stringent or less highly stringent, as described above. In instances where the nucleic acid molecules are deoxyoligonucleotides ("DNA oligos"), such molecules are generally about 16 to about 100 bases long, or about 20 to about 80, or about 34 to about 45 bases long, or any variation or combination of sizes represented therein that incorporate a contiguous region of sequence first disclosed in the Sequence Listing. Such oligonucleotides can be used in conjunction with the polymerase chain reaction (PCR) to screen libraries, isolate clones, and prepare cloning and sequencing templates, etc.

Alternatively, such NHP oligonucleotides can be used as hybridization probes for screening libraries, and assessing gene expression patterns (particularly using a micro array or high-throughput "chip" format). Additionally, a series of the described NHP oligonucleotide sequences, or the complements thereof, can be used to represent all or a portion of the described NHP sequences. An oligonucleotide or polynucleotide sequence first disclosed in at least a portion of one or more of the sequences of SEQ ID NOS: 1-15 can be used as a hybridization probe in conjunction with a solid support matrix/substrate (resins, beads, membranes, plastics, polymers, metal or metallized substrates, crystalline or polycrystalline substrates, etc.). Of particular note are spatially addressable arrays (*i.e.*, gene chips, microtiter plates, etc.) of oligonucleotides and polynucleotides, or corresponding oligopeptides and polypeptides, wherein at least one of the biopolymers present on the spatially addressable array comprises an oligonucleotide or polynucleotide

sequence first disclosed in at least one of the sequences of SEQ ID NOS: 1-15, or an amino acid sequence encoded thereby. Methods for attaching biopolymers to, or synthesizing biopolymers on, solid support matrices, and conducting binding studies thereon are disclosed in, *inter alia*, U.S. Patent Nos. 5,700,637, 5,556,752, 5,744,305, 4,631,211, 5,445,934, 5,252,743, 4,713,326, 5,424,186, and 4,689,405 the disclosures of which are herein incorporated by reference in their entirety.

Addressable arrays comprising sequences first disclosed in SEQ ID NOS:1-15 can be used to identify and characterize the temporal and tissue specific expression of a gene. These addressable arrays incorporate oligonucleotide sequences of sufficient length to confer the required specificity, yet be within the limitations of the production technology. The length of these probes is within a range of between about 8 to about 2000 nucleotides. Preferably the probes consist of 60 nucleotides and more preferably 25 nucleotides from the sequences first disclosed in SEQ ID NOS:1-15.

For example, a series of the described oligonucleotide sequences, or the complements thereof, can be used in chip format to represent all or a portion of the described sequences. The oligonucleotides, typically between about 16 to about 40 (or any whole number within the stated range) nucleotides in length can partially overlap each other and/or the sequence may be represented using oligonucleotides that do not overlap. Accordingly, the described polynucleotide sequences shall typically comprise at least about two or three distinct oligonucleotide sequences of at least about 8 nucleotides in length that are each first disclosed in the described Sequence Listing. Such oligonucleotide sequences can begin at any nucleotide present within a sequence in the Sequence Listing and proceed in either a sense (5'-to-3') orientation vis-a-vis the described sequence or in an antisense orientation.

Microarray-based analysis allows the discovery of broad patterns of genetic activity, providing new understanding of gene functions and generating novel and unexpected insight into transcriptional processes and biological mechanisms. The use of addressable arrays comprising sequences first disclosed in SEQ ID NOS:1-15 provides detailed information about transcriptional changes involved in a specific pathway, potentially leading to the identification of novel components or gene functions that manifest themselves as novel phenotypes.

Probes consisting of sequences first disclosed in SEQ ID NOS:1-15 can also be used in the identification, selection and validation of novel molecular targets for drug discovery. The use of these unique sequences permits the direct confirmation of drug targets and recognition of drug dependent changes in gene expression that are modulated through pathways distinct from the drugs intended target. These unique sequences therefore also have utility in defining and monitoring both drug action and toxicity.

As an example of utility, the sequences first disclosed in SEQ ID NOS:1-15 can be utilized in microarrays or other assay formats, to screen collections of genetic material from patients who have a particular medical condition. These investigations can also be carried out using the sequences first disclosed in SEQ ID NOS:1-15 *in silico* and by comparing previously collected genetic databases and the disclosed sequences using computer software known to those in the art.

Thus the sequences first disclosed in SEQ ID NOS:1-15 can be used to identify mutations associated with a particular disease and also as a diagnostic or prognostic assay.

Although the presently described sequences have been specifically described using nucleotide sequence, it should be appreciated that each of the sequences can uniquely be described using any of a wide variety of additional structural attributes, or combinations thereof. For example, a given sequence can be

described by the net composition of the nucleotides present within a given region of the sequence in conjunction with the presence of one or more specific oligonucleotide sequence(s) first disclosed in the SEQ ID NOS: 1-15. Alternatively, a restriction map specifying the relative positions of restriction endonuclease digestion sites, or various palindromic or other specific oligonucleotide sequences can be used to structurally describe a given sequence. Such restriction maps, which are typically generated by widely available computer programs (*e.g.*, the University of Wisconsin GCG sequence analysis package, SEQUENCHER 3.0, Gene Codes Corp., Ann Arbor, MI, etc.), can optionally be used in conjunction with one or more discrete nucleotide sequence(s) present in the sequence that can be described by the relative position of the sequence relatve to one or more additional sequence(s) or one or more restriction sites present in the disclosed sequence.

For oligonucleotide probes, highly stringent conditions may refer, for example, to washing in 6xSSC/0.05% sodium pyrophosphate at 37°C (for 14-base oligos), 48°C (for 17-base oligos), 55°C (for 20-base oligos), and 60°C (for 23-base oligos). These nucleic acid molecules may encode or act as NHP gene antisense molecules, useful, for example, in NHP gene regulation (for and/or as antisense primers in amplification reactions of NHP nucleic acid sequences). With respect to NHP gene regulation, such techniques can be used to regulate biological functions. Further, such sequences may be used as part of ribozyme and/or triple helix sequences that are also useful for NHP gene regulation.

Inhibitory antisense or double stranded oligonucleotides can additionally comprise at least one modified base moiety which is selected from the group including but not limited to 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine,

5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

The antisense oligonucleotide can also comprise at least one modified sugar moiety selected from the group including but not limited to arabinose, 2-fluoroarabinose, xylulose, and hexose.

In yet another embodiment, the antisense oligonucleotide will comprise at least one modified phosphate backbone selected from the group consisting of a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or analog thereof.

In yet another embodiment, the antisense oligonucleotide is an α-anomeric oligonucleotide. An α-anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual β-units, the strands run parallel to each other (Gautier *et al.*, 1987, Nucl. Acids Res. *15*:6625-6641). The oligonucleotide is a 2'-0-methylribonucleotide (Inoue *et al.*, 1987, Nucl. Acids Res. *15*:6131-6148), or a chimeric RNA-DNA analogue (Inoue *et al.*, 1987, FEBS Lett. *215*:327-330). Alternatively, double stranded RNA can be used to disrupt the expression and function of a targeted NHP.

Oligonucleotides of the invention can be synthesized by standard methods known in the art, *e.g.* by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides can be synthesized by the method of Stein *et al.* (1988, Nucl. Acids Res. *16*:3209), and methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin *et al.*, 1988, Proc. Natl. Acad. Sci. U.S.A. *85*:7448-7451), etc.

Low stringency conditions are well known to those of skill in the art, and will vary predictably depending on the specific organisms from which the library and the labeled sequences are derived. For guidance regarding such conditions see, for example, Sambrook *et al.*, 1989, Molecular Cloning, A Laboratory Manual (and periodic updates thereof), Cold Springs Harbor Press, N.Y.; and Ausubel *et al.*, 1989, Current Protocols in Molecular Biology, Green Publishing Associates and Wiley Interscience, N.Y.

Alternatively, suitably labeled NHP nucleotide probes can be used to screen a human genomic library using appropriately stringent conditions or by PCR. The identification and characterization of human genomic clones is helpful for identifying polymorphisms (including, but not limited to, nucleotide repeats, microsatellite alleles, single nucleotide polymorphisms, or coding single nucleotide polymorphisms), determining the genomic structure of a given locus/allele, and designing diagnostic tests. For example, sequences derived from regions adjacent to the intron/exon boundaries of the human gene can be used to design primers for use in amplification assays to detect mutations within the exons, introns, splice sites (*e.g.*, splice acceptor and/or donor sites), etc., that can be used in diagnostics and pharmacogenomics.

Further, a NHP homolog can be isolated from nucleic acid from an organism of interest by performing PCR using two degenerate or

"wobble" oligonucleotide primer pools designed on the basis of amino acid sequences within the NHP products disclosed herein. The template for the reaction may be total RNA, mRNA, and/or cDNA obtained by reverse transcription of mRNA prepared from human or non-human cell lines or tissue known or suspected to express an allele of a NHP gene.

The PCR product can be subcloned and sequenced to ensure that the amplified sequences represent the sequence of the desired NHP sequence. The PCR fragment can then be used to isolate a full length cDNA clone by a variety of methods. For example, the amplified fragment can be labeled and used to screen a cDNA library, such as a bacteriophage cDNA library. Alternatively, the labeled fragment can be used to isolate genomic clones via the screening of a genomic library.

PCR technology can also be used to isolate full length cDNA sequences. For example, RNA can be isolated, following standard procedures, from an appropriate cellular or tissue source (*i.e.*, one known, or suspected, to express a NHP sequence, such as, for example, testis tissue). A reverse transcription (RT) reaction can be performed on the RNA using an oligonucleotide primer specific for the most 5' end of the amplified fragment for the priming of first strand synthesis. The resulting RNA/DNA hybrid may then be "tailed" using a standard terminal transferase reaction, the hybrid may be digested with RNase H, and second strand synthesis may then be primed with a complementary primer. Thus, cDNA sequences upstream of the amplified fragment can be isolated. For a review of cloning strategies that can be used, see *e.g.*, Sambrook *et al.*, 1989, *supra*.

A cDNA encoding a mutant NHP sequence can be isolated, for example, by using PCR. In this case, the first cDNA strand may be synthesized by hybridizing an oligo-dT oligonucleotide to mRNA isolated from tissue known or suspected to be expressed in an individual putatively carrying a mutant NHP allele, and by

extending the new strand with reverse transcriptase. The second strand of the cDNA is then synthesized using an oligonucleotide that hybridizes specifically to the 5′ end of the normal gene. Using these two primers, the product is then amplified via PCR, optionally cloned into a suitable vector, and subjected to DNA sequence analysis through methods well known to those of skill in the art. By comparing the DNA sequence of the mutant NHP allele to that of a corresponding normal NHP allele, the mutation(s) responsible for the loss or alteration of function of the mutant NHP gene product can be ascertained.

Alternatively, a genomic library can be constructed using DNA obtained from an individual suspected of or known to carry a mutant NHP allele (*e.g.*, a person manifesting a NHP-associated phenotype such as, for example, obesity, high blood pressure, connective tissue disorders, infertility, etc.), or a cDNA library can be constructed using RNA from a tissue known, or suspected, to express a mutant NHP allele. A normal NHP sequence, or any suitable fragment thereof, can then be labeled and used as a probe to identify the corresponding mutant NHP allele in such libraries. Clones containing mutant NHP sequences can then be purified and subjected to sequence analysis according to methods well known to those skilled in the art.

Additionally, an expression library can be constructed utilizing cDNA synthesized from, for example, RNA isolated from a tissue known, or suspected, to express a mutant NHP allele in an individual suspected of or known to carry such a mutant allele. In this manner, gene products made by the putatively mutant tissue can be expressed and screened using standard antibody screening techniques in conjunction with antibodies raised against normal NHP product, as described below. (For screening techniques, see, for example, Harlow, E. and Lane, eds., 1988, "Antibodies: A Laboratory Manual", Cold Spring Harbor Press, Cold Spring Harbor.)

Additionally, screening can be accomplished by screening with labeled NHP fusion proteins, such as, for example, alkaline phosphatase-NHP or NHP-alkaline phosphatase fusion proteins. In cases where a NHP mutation results in an expressed gene product with altered function (*e.g.*, as a result of a missense or a frameshift mutation), polyclonal antibodies to NHP are likely to cross-react with a corresponding mutant NHP gene product. Library clones detected via their reaction with such labeled antibodies can be purified and subjected to sequence analysis according to methods well known in the art.

The invention also encompasses (a) DNA vectors that contain any of the foregoing NHP coding sequences and/or their complements (*i.e.*, antisense); (b) DNA expression vectors that contain any of the foregoing NHP coding sequences operatively associated with a regulatory element that directs the expression of the coding sequences (for example, baculo virus as described in U.S. Patent No. 5,869,336 herein incorporated by reference); (c) genetically engineered host cells that contain any of the foregoing NHP coding sequences operatively associated with a regulatory element that directs the expression of the coding sequences in the host cell; and (d) genetically engineered host cells that express an endogenous NHP sequence under the control of an exogenously introduced regulatory element (*i.e.*, gene activation). As used herein, regulatory elements include, but are not limited to, inducible and non-inducible promoters, enhancers, operators and other elements known to those skilled in the art that drive and regulate expression. Such regulatory elements include but are not limited to the cytomegalovirus (hCMV) immediate early gene, regulatable, viral elements (particularly retroviral LTR promoters), the early or late promoters of SV40 adenovirus, the *lac* system, the *trp* system, the *TAC* system, the *TRC* system, the major operator and promoter regions of phage lambda, the control regions of fd coat protein, the promoter for 3-phosphoglycerate

kinase (PGK), the promoters of acid phosphatase, and the promoters of the yeast α-mating factors.

The present invention also encompasses antibodies and anti-idiotypic antibodies (including Fab fragments), antagonists and agonists of a NHP, as well as compounds or nucleotide constructs that inhibit expression of a NHP gene (transcription factor inhibitors, antisense and ribozyme molecules, or gene or regulatory sequence replacement constructs), or promote the expression of a NHP (*e.g.*, expression constructs in which NHP coding sequences are operatively associated with expression control elements such as promoters, promoter/enhancers, etc.).

The NHPs or NHP peptides, NHP fusion proteins, NHP nucleotide sequences, antibodies, antagonists and agonists can be useful for the detection of mutant NHPs or inappropriately expressed NHPs for the diagnosis of disease. The NHP proteins or peptides, NHP fusion proteins, NHP nucleotide sequences, host cell expression systems, antibodies, antagonists, agonists and genetically engineered cells and animals can be used for screening for drugs (or high throughput screening of combinatorial libraries) effective in the treatment of the symptomatic or phenotypic manifestations of perturbing the normal function of a NHP in the body. The use of engineered host cells and/or animals may offer an advantage in that such systems allow not only for the identification of compounds that bind to the endogenous receptor for a NHP, but can also identify compounds that trigger NHP-mediated activities or pathways.

Finally, the NHP products can be used as therapeutics. For example, soluble derivatives such as NHP peptides/domains corresponding to NHP, NHP fusion protein products (especially NHP-Ig fusion proteins, *i.e.*, fusions of a NHP, or a domain of a NHP, to an IgFc), NHP antibodies and anti-idiotypic antibodies (including Fab fragments), antagonists or agonists (including compounds that modulate or act on downstream targets in a NHP-

mediated pathway) can be used to directly treat diseases or disorders. For instance, the administration of an effective amount of soluble NHP, or a NHP-IgFc fusion protein or an anti-idiotypic antibody (or its Fab) that mimics the NHP could activate or effectively antagonize the endogenous NHP receptor. Nucleotide constructs encoding such NHP products can be used to genetically engineer host cells to express such products *in vivo*; these genetically engineered cells function as "bioreactors" in the body delivering a continuous supply of a NHP, a NHP peptide, or a NHP fusion protein to the body. Nucleotide constructs encoding functional NHP, mutant NHPs, as well as antisense and ribozyme molecules can also be used in "gene therapy" approaches for the modulation of NHP expression. Thus, the invention also encompasses pharmaceutical formulations and methods for treating biological disorders.

Various aspects of the invention are described in greater detail in the subsections below.

5.1 THE NHP SEQUENCES

The cDNA sequences and the corresponding deduced amino acid sequences of the described NHP are presented in the Sequence Listing. SEQ ID NOS:15 describes the NHP ORFs as well as flanking regions. The NHP nucleotides were obtained from human cDNA libraries using probes and/or primers generated from human gene trapped sequence tags. Expression analysis has provided evidence that the described NHP can be expressed in a variety of human cells as well as gene trapped human cells.

5.2 NHP AND NHP POLYPEPTIDES

NHPs, polypeptides, peptide fragments, mutated, truncated, or deleted forms of the NHPs, and/or NHP fusion proteins can be prepared for a variety of uses. These uses include, but are not limited to, the generation of antibodies, as reagents in

diagnostic assays, for the identification of other cellular gene products related to a NHP, as reagents in assays for screening for compounds that can be as pharmaceutical reagents useful in the therapeutic treatment of mental, biological, or medical disorders and disease.

The Sequence Listing discloses the amino acid sequence encoded by the described NHP polynucleotides. The NHPs display initiator methionines in DNA sequence contexts consistent with translation initiation sites, and apparently display signal sequences which can indicate that the described NHP ORFs are secreted proteins or possibly membrane associated.

The NHP amino acid sequences of the invention include the amino acid sequences presented in the Sequence Listing as well as analogues and derivatives thereof, as well as any oligopeptide sequence of at least about 10-40, generally about 12-35, or about 16-30 amino acids in length first disclosed in the Sequence Listing. Further, corresponding NHP homologues from other species are encompassed by the invention. In fact, any NHP encoded by the NHP nucleotide sequences described above are within the scope of the invention, as are any novel polynucleotide sequences encoding all or any novel portion of an amino acid sequence presented in the Sequence Listing. The degenerate nature of the genetic code is well known, and, accordingly, each amino acid presented in the Sequence Listing, is generically representative of the well known nucleic acid "triplet" codon, or in many cases codons, that can encode the amino acid. As such, as contemplated herein, the amino acid sequences presented in the Sequence Listing, when taken together with the genetic code (see, for example, Table 4-1 at page 109 of "Molecular Cell Biology", 1986, J. Darnell *et al.* eds., Scientific American Books, New York, NY, herein incorporated by reference) are generically representative of all the various permutations and combinations of nucleic acid sequences that can encode such amino acid sequences.

The invention also encompasses proteins that are functionally equivalent to the NHPs encoded by the presently described nucleotide sequences as judged by any of a number of criteria, including, but not limited to, the ability to bind and cleave a substrate of a NHP, or the ability to effect an identical or complementary downstream pathway, or a change in cellular metabolism (*e.g.*, proteolytic activity, ion flux, tyrosine phosphorylation, etc.). Such functionally equivalent NHP proteins include, but are not limited to, additions or substitutions of amino acid residues within the amino acid sequence encoded by the NHP nucleotide sequences described above, but which result in a silent change, thus producing a functionally equivalent gene product. Amino acid substitutions can be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues involved. For example, nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan, and methionine; polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine, and glutamine; positively charged (basic) amino acids include arginine, lysine, and histidine; and negatively charged (acidic) amino acids include aspartic acid and glutamic acid.

A variety of host-expression vector systems can be used to express the NHP nucleotide sequences of the invention. Where, as in the present instance, the NHP products or NHP polypeptides can be produced in soluble or secreted forms (by removing one or more transmembrane domains where applicable), the peptide or polypeptide can be recovered from the culture media. Such expression systems also encompass engineered host cells that express a NHP, or a functional equivalent, *in situ*. Purification or enrichment of NHP from such expression systems can be accomplished using appropriate detergents and lipid micelles and methods well known to those skilled in the art. However, such

engineered host cells themselves may be used in situations where it is important not only to retain the structural and functional characteristics of the NHP, but to assess biological activity, *e.g.*, in drug screening assays.

The expression systems that may be used for purposes of the invention include but are not limited to microorganisms such as bacteria (*e.g.*, *E. coli*, *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing NHP nucleotide sequences; yeast (*e.g.*, *Saccharomyces*, *Pichia*) transformed with recombinant yeast expression vectors containing NHP encoding nucleotide sequences; insect cell systems infected with recombinant virus expression vectors (*e.g.*, baculovirus) containing NHP sequences; plant cell systems infected with recombinant virus expression vectors (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (*e.g.*, Ti plasmid) containing NHP nucleotide sequences; or mammalian cell systems (*e.g.*, COS, CHO, BHK, 293, 3T3) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (*e.g.*, metallothionein promoter) or from mammalian viruses (*e.g.*, the adenovirus late promoter; the vaccinia virus 7.5K promoter).

In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the NHP product being expressed. For example, when a large quantity of such a protein is to be produced for the generation of pharmaceutical compositions of or containing NHP, or for raising antibodies to a NHP, vectors that direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the *E. coli* expression vector pUR278 (Ruther *et al.*, 1983, EMBO J. *2*:1791), in which a NHP coding sequence may be ligated

individually into the vector in frame with the *lacZ* coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, 1985, Nucleic Acids Res. *13*:3101-3109; Van Heeke & Schuster, 1989, J. Biol. Chem. *264*:5503-5509); and the like. pGEX vectors (Pharmacia or American Type Culture Collection) can also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption to glutathione-agarose beads followed by elution in the presence of free glutathione. The PGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

In an insect system, *Autographa californica* nuclear polyhidrosis virus (AcNPV) is used as a vector to express foreign sequences. The virus grows in *Spodoptera frugiperda* cells. A NHP coding sequence can be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter). Successful insertion of NHP coding sequence will result in inactivation of the polyhedrin gene and production of non-occluded recombinant virus (*i.e.*, virus lacking the proteinaceous coat coded for by the polyhedrin gene). These recombinant viruses are then used to infect Spodoptera frugiperda cells in which the inserted sequence is expressed (*e.g.*, see Smith *et al.*, 1983, J. Virol. 46: 584; Smith, U.S. Patent No. 4,215,051).

In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the NHP nucleotide sequence of interest may be ligated to an adenovirus transcription/translation control complex, *e.g.*, the late promoter and tripartite leader sequence. This chimeric sequence may then be inserted in the adenovirus genome by *in vitro* or *in vivo* recombination. Insertion in a non-

essential region of the viral genome (*e.g.*, region E1 or E3) will result in a recombinant virus that is viable and capable of expressing a NHP product in infected hosts (*e.g.*, See Logan & Shenk, 1984, Proc. Natl. Acad. Sci. USA *81*:3655-3659). Specific initiation signals may also be required for efficient translation of inserted NHP nucleotide sequences. These signals include the ATG initiation codon and adjacent sequences. In cases where an entire NHP sequence or cDNA, including its own initiation codon and adjacent sequences, is inserted into the appropriate expression vector, no additional translational control signals may be needed. However, in cases where only a portion of a NHP coding sequence is inserted, exogenous translational control signals, including, perhaps, the ATG initiation codon, must be provided. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (See Bittner *et al.*, 1987, Methods in Enzymol. *153*:516-544).

In addition, a host cell strain may be chosen that modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (*e.g.*, glycosylation) and processing (*e.g.*, cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript,

glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include, but are not limited to, CHO, VERO, BHK, HeLa, COS, MDCK, 293, 3T3, WI38, and in particular, human cell lines.

For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the NHP sequences described above can be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (*e.g.*, promoter, enhancer sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the NHP product. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that affect the endogenous activity of the NHP product.

A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler, *et al.*, 1977, Cell *11*:223), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, 1962, Proc. Natl. Acad. Sci. USA *48*:2026), and adenine phosphoribosyltransferase (Lowy, *et al.*, 1980, Cell *22*:817) genes can be employed in tk^-, $hgprt^-$ or $aprt^-$ cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler, *et al.*, 1980, Natl. Acad. Sci. USA 77:3567; O'Hare, *et al.*, 1981, Proc. Natl. Acad. Sci. USA *78*:1527); gpt,

which confers resistance to mycophenolic acid (Mulligan & Berg, 1981, Proc. Natl. Acad. Sci. USA *78*:2072); neo, which confers resistance to the aminoglycoside G-418 (Colberre-Garapin, *et al.*, 1981, J. Mol. Biol. *150*:1); and hygro, which confers resistance to hygromycin (Santerre, *et al.*, 1984, Gene *30*:147).

Alternatively, any fusion protein can be readily purified by utilizing an antibody specific for the fusion protein being expressed. For example, a system described by Janknecht *et al.* allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht, *et al.*, 1991, Proc. Natl. Acad. Sci. USA *88*:8972-8976). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the gene's open reading frame is translationally fused to an amino-terminal tag consisting of six histidine residues. Extracts from cells infected with recombinant vaccinia virus are loaded onto Ni^{2+}·nitriloacetic acid-agarose columns and histidine-tagged proteins are selectively eluted with imidazole-containing buffers.

Also encompassed by the present invention are fusion proteins that direct the NHP to a target organ and/or facilitate transport across the membrane into the cytosol. Conjugation of NHPs to antibody molecules or their Fab fragments could be used to target cells bearing a particular epitope. Attaching the appropriate signal sequence to the NHP would also transport the NHP to the desired location within the cell. Alternatively targeting of NHP or its nucleic acid sequence might be achieved using liposome or lipid complex based delivery systems. Such technologies are described in Liposomes:A Practical Approach, New,RRC ed., Oxford University Press, New York and in U.S. Patents Nos. 4,594,595, 5,459,127, 5,948,767 and 6,110,490 and their respective disclosures which are herein incorporated by reference in their entirety. Additionally embodied are novel protein constructs engineered in such a way that they facilitate transport of the NHP to the target site or desired organ, where they cross the cell

membrane and/or the nucleus where the NHP can exert its functional activity. This goal may be achieved by coupling of the NHP to a cytokine or other ligand that provides targeting specificity, and/or to a protein transducing domain (see generally U.S. applications Ser. No. 60/111,701 and 60/056,713, both of which are herein incorporated by reference, for examples of such transducing sequences) to facilitate passage across cellular membranes and can optionally be engineered to include nuclear localization sequences.

5.3 ANTIBODIES TO NHP PRODUCTS

Antibodies that specifically recognize one or more epitopes of a NHP, or epitopes of conserved variants of a NHP, or peptide fragments of a NHP are also encompassed by the invention. Such antibodies include but are not limited to polyclonal antibodies, monoclonal antibodies (mAbs), humanized or chimeric antibodies, single chain antibodies, Fab fragments, $F(ab')_2$ fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments of any of the above.

The antibodies of the invention may be used, for example, in the detection of NHP in a biological sample and may, therefore, be utilized as part of a diagnostic or prognostic technique whereby patients may be tested for abnormal amounts of NHP. Such antibodies may also be utilized in conjunction with, for example, compound screening schemes for the evaluation of the effect of test compounds on expression and/or activity of a NHP gene product. Additionally, such antibodies can be used in conjunction gene therapy to, for example, evaluate the normal and/or engineered NHP-expressing cells prior to their introduction into the patient. Such antibodies may additionally be used as a method for the inhibition of abnormal NHP activity. Thus, such antibodies may, therefore, be utilized as part of treatment methods.

For the production of antibodies, various host animals may be immunized by injection with the NHP, an NHP peptide (*e.g.*, one corresponding to a functional domain of an NHP), truncated NHP polypeptides (NHP in which one or more domains have been deleted), functional equivalents of the NHP or mutated variant of the NHP. Such host animals may include but are not limited to pigs, rabbits, mice, goats, and rats, to name but a few. Various adjuvants may be used to increase the immunological response, depending on the host species, including but not limited to Freund's adjuvant (complete and incomplete), mineral salts such as aluminum hydroxide or aluminum phosphate, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and *Corynebacterium parvum*. Alternatively, the immune response could be enhanced by combination and or coupling with molecules such as keyhole limpet hemocyanin, tetanus toxoid, diptheria toxoid, ovalbumin, cholera toxin or fragments thereof. Polyclonal antibodies are heterogeneous populations of antibody molecules derived from the sera of the immunized animals.

Monoclonal antibodies, which are homogeneous populations of antibodies to a particular antigen, can be obtained by any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique of Kohler and Milstein, (1975, Nature *256*:495-497; and U.S. Patent No. 4,376,110), the human B-cell hybridoma technique (Kosbor *et al.*, 1983, Immunology Today *4*:72; Cole *et al.*, 1983, Proc. Natl. Acad. Sci. USA *80*:2026-2030), and the EBV-hybridoma technique (Cole *et al.*, 1985, Monoclonal Antibodies And Cancer Therapy, Alan R. Liss, Inc., pp. 77-96). Such antibodies may be of any immunoglobulin class including IgG, IgM, IgE, IgA, IgD and any subclass thereof. The hybridoma producing the mAb of this invention may be cultivated *in vitro* or

in vivo. Production of high titers of mAbs in vivo makes this the presently preferred method of production.

In addition, techniques developed for the production of "chimeric antibodies" (Morrison *et al.*, 1984, Proc. Natl. Acad. Sci., *81*:6851-6855; Neuberger *et al.*, 1984, Nature, *312*:604-608; Takeda *et al.*, 1985, Nature, *314*:452-454) by splicing the genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used. A chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region. Such technologies are described in U.S. Patents Nos. 6,075,181 and 5,877,397 and their respective disclosures which are herein incorporated by reference in their entirety. Also favored is the production of fully humanized monoclonal antibodies as described in US Patent No. 6,150,584 and respective disclosures which are herein incorporated by reference in their entirety.

Alternatively, techniques described for the production of single chain antibodies (U.S. Patent 4,946,778; Bird, 1988, Science *242*:423-426; Huston *et al.*, 1988, Proc. Natl. Acad. Sci. USA *85*:5879-5883; and Ward *et al.*, 1989, Nature *334*:544-546) can be adapted to produce single chain antibodies against NHP gene products. Single chain antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide.

Antibody fragments which recognize specific epitopes may be generated by known techniques. For example, such fragments include, but are not limited to: the $F(ab')_2$ fragments which can be produced by pepsin digestion of the antibody molecule and the Fab fragments which can be generated by reducing the disulfide bridges of the $F(ab')_2$ fragments. Alternatively, Fab expression libraries may be constructed (Huse *et al.*, 1989, Science,

246:1275-1281) to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity.

Antibodies to a NHP can, in turn, be utilized to generate anti-idiotype antibodies that "mimic" a given NHP, using techniques well known to those skilled in the art. (See, *e.g.*, Greenspan & Bona, 1993, FASEB J *7(5)*:437-444; and Nissinoff, 1991, J. Immunol. *147(8)*:2429-2438). For example antibodies which bind to a NHP domain and competitively inhibit the binding of NHP to its cognate receptor can be used to generate anti-idiotypes that "mimic" the NHP and, therefore, bind and activate or neutralize a receptor. Such anti-idiotypic antibodies or Fab fragments of such anti-idiotypes can be used in therapeutic regimens involving a NHP signaling pathway.

The present invention is not to be limited in scope by the specific embodiments described herein, which are intended as single illustrations of individual aspects of the invention, and functionally equivalent methods and components are within the scope of the invention. Indeed, various modifications of the invention, in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the appended claims. All cited publications, patents, and patent applications are herein incorporated by reference in their entirety.

WHAT IS CLAIMED IS:

1. An isolated nucleic acid molecule comprising at least 24 contiguous bases of nucleotide sequence first disclosed in SEQ ID NO: 1.

2. An isolated nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the amino acid sequence shown in SEQ ID NO: 2; and

(b) hybridizes under stringent conditions to the nucleotide sequence of SEQ ID NO: 1 or the complement thereof.

3. An isolated nucleic acid molecule encoding the amino acid sequence described in SEQ ID NO: 2.

4. An isolated oligopeptide comprising at least about 12 amino acids in a sequence first disclosed in SEQ ID NO:2.

ABSTRACT

Novel human polynucleotide and polypeptide sequences are disclosed that can be used in therapeutic, diagnostic, and pharmacogenomic applications.

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION

ATTORNEY DOCKET NO. LEX-0118-USA

As a below named inventor, I hereby declare that:

My residence/post office address and citizenship are as stated below next to my name;

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Novel Human Enzymes and Polynucleotides Encoding the Same

the specification of which is attached hereto unless the following box is checked:

( ) was filed on _____ as US Application Serial No. or PCT International Application Number _____ and was amended on _____ (if applicable).

I hereby state that I have reviewed and understood the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above. I acknowledge the duty to disclose all information which is material to patentability as defined in 37 CFR 1.56.

Foreign Application(s) and/or Claim of Foreign Priority

I hereby claim foreign priority benefits under Title 35, United States Code Section 119 of any foreign application(s) for patent or inventor(s) certificate listed below and have also identified below any foreign application for patent or inventor(s) certificate having a filing date before that of the application on which priority is claimed:

COUNTRY	APPLICATION NUMBER	DATE FILED	PRIORITY CLAIMED UNDER 35 U.S.C. 119
			YES:___ NO:___
			YES:___ NO:___

Provisional Application

I hereby claim the benefit under Title 35, United States Code Section 119(e) of any United States provisional application(s) listed below:

APPLICATION SERIAL NUMBER	FILING DATE
60/179,000	1/28/2000

U.S. Priority Claim

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

APPLICATION SERIAL NUMBER	FILING DATE	STATUS(patented/pending/abandoned)

POWER OF ATTORNEY:

As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) listed below to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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_____ _____

Inventor's Signature **Date**

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<213> Homo sapiens

<400> 3

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gcttttaatc tgaccactgg accagcccat tgggagttac ttcagcgaag ccgggctgtt     240
gataatcagg tgtatgtggc cacagcctct cctgcccggg atgacaaagc ctcctatgtt     300
gcctggggac acagcaccgt ggtgaaccct tgggggggagg ttctagccaa agctggcaca     360
gaagaagcaa tcgtgtattc agacatagac ctgaagaagc tggctgaaat acgccagcaa     420
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<210> 4
<211> 159
<212> PRT
<213> Homo sapiens

<400> 4

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Phe His Leu Cys Ile Phe Cys Leu Glu Thr Ala Tyr Cys Arg Val Gly
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            20                  25                  30
Leu Gly Ile Cys Tyr Asp Met Arg Phe Ala Glu Leu Ala Gln Ile Tyr
        35                  40                  45
Ala Gln Arg Gly Cys Gln Leu Leu Val Tyr Pro Gly Ala Phe Asn Leu
    50                  55                  60
Thr Thr Gly Pro Ala His Trp Glu Leu Leu Gln Arg Ser Arg Ala Val
65                  70                  75                  80
Asp Asn Gln Val Tyr Val Ala Thr Ala Ser Pro Ala Arg Asp Asp Lys
                85                  90                  95
Ala Ser Tyr Val Ala Trp Gly His Ser Thr Val Val Asn Pro Trp Gly
            100                 105                 110
Glu Val Leu Ala Lys Ala Gly Thr Glu Glu Ala Ile Val Tyr Ser Asp
        115                 120                 125
Ile Asp Leu Lys Lys Leu Ala Glu Ile Arg Gln Gln Ile Pro Val Phe
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Arg Gln Lys Arg Ser Asp Leu Tyr Ala Val Glu Met Lys Lys Pro
145                 150                 155
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<210> 5
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<212> DNA
<213> Homo sapiens

<400> 5

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gctgttgata atcaggtgta tgtggccaca gcctctcctg cccgggatga caaagcctcc     180
tatgttgcct ggggacacag caccgtggtg aacccttggg gggaggttct agccaaagct     240
ggcacagaag aagcaatcgt gtattcagac atagacctga agaagctggc tgaaatacgc     300
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<211> 121
<212> PRT
<213> Homo sapiens

<400> 6

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Trp Glu Leu Leu Gln Arg Ser Arg Ala Val Asp Asn Gln Val Tyr Val
        35                  40                  45
Ala Thr Ala Ser Pro Ala Arg Asp Asp Lys Ala Ser Tyr Val Ala Trp
    50                  55                  60
Gly His Ser Thr Val Val Asn Pro Trp Gly Glu Val Leu Ala Lys Ala
65                  70                  75                  80
Gly Thr Glu Glu Ala Ile Val Tyr Ser Asp Ile Asp Leu Lys Lys Leu
                85                  90                  95
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            100                 105                 110
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<210> 7

<211> 507
<212> DNA
<213> Homo sapiens

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gcttttaatc tgaccactgg accagcccat tgggagttac ttcagcgaag ccgggctgtt 240
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gaagaagcaa tcgtgtattc agacatagac ctgaagaagc tggctgaaat acgccagcaa 420
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<210> 8
<211> 168
<212> PRT
<213> Homo sapiens

<400> 8
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35 40 45
Ala Gln Arg Gly Cys Gln Leu Leu Val Tyr Pro Gly Ala Phe Asn Leu
50 55 60
Thr Thr Gly Pro Ala His Trp Glu Leu Leu Gln Arg Ser Arg Ala Val
65 70 75 80
Asp Asn Gln Val Tyr Val Ala Thr Ala Ser Pro Ala Arg Asp Asp Lys
85 90 95
Ala Ser Tyr Val Ala Trp Gly His Ser Thr Val Val Asn Pro Trp Gly
100 105 110
Glu Val Leu Ala Lys Ala Gly Thr Glu Glu Ala Ile Val Tyr Ser Asp
115 120 125
Ile Asp Leu Lys Lys Leu Ala Glu Ile Arg Gln Gln Ile Pro Val Phe
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Asn Pro His Arg Ser Phe Leu Lys
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<211> 393
<212> DNA
<213> Homo sapiens

<400> 9
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<210> 10
<211> 130
<212> PRT
<213> Homo sapiens

<400> 10

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		20					25					30			
Trp	Glu	Leu	Leu	Gln	Arg	Ser	Arg	Ala	Val	Asp	Asn	Gln	Val	Tyr	Val
	35					40					45				
Ala	Thr	Ala	Ser	Pro	Ala	Arg	Asp	Asp	Lys	Ala	Ser	Tyr	Val	Ala	Trp
50					55					60					
Gly	His	Ser	Thr	Val	Val	Asn	Pro	Trp	Gly	Glu	Val	Leu	Ala	Lys	Ala
65				70					75						80
Gly	Thr	Glu	Glu	Ala	Ile	Val	Tyr	Ser	Asp	Ile	Asp	Leu	Lys	Lys	Leu
			85					90					95		
Ala	Glu	Ile	Arg	Gln	Gln	Ile	Pro	Val	Phe	Arg	Gln	Lys	Arg	Asn	Ile
		100					105					110			
Phe	Leu	Asn	Met	Gln	Arg	Lys	Phe	Leu	Val	Asn	Pro	His	Arg	Ser	Phe
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Leu	Lys														
130															

<210> 11
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<212> DNA
<213> Homo sapiens

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<210> 12
<211> 152
<212> PRT
<213> Homo sapiens

<400> 12

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Lys	Ser	Asp	Asn	Val	Thr	Arg	Ala	Cys	Ser	Phe	Ile	Arg	Glu	Ala	Ala
		20					25					30			
Thr	Gln	Gly	Ala	Lys	Ile	Val	Ser	Leu	Pro	Glu	Cys	Phe	Asn	Ser	Pro
	35					40					45				
Tyr	Gly	Ala	Lys	Tyr	Phe	Pro	Glu	Tyr	Ala	Glu	Lys	Ile	Pro	Gly	Glu
50					55					60					

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Ser Thr Gln Lys Leu Ser Glu Val Ala Lys Glu Cys Ser Ile Tyr Leu
65                  70                  75                  80
Ile Gly Gly Ser Ile Pro Glu Glu Asp Ala Gly Lys Leu Tyr Asn Thr
                85                  90                  95
Cys Ala Val Phe Gly Pro Asp Gly Thr Leu Leu Ala Lys Tyr Arg Lys
            100                 105                 110
Ile His Leu Phe Asp Ile Asp Val Pro Gly Lys Ile Thr Phe Gln Glu
        115                 120                 125
Ser Lys Thr Leu Ser Pro Gly Asp Ser Phe Ser Thr Phe Asp Thr Arg
    130                 135                 140
Met Tyr Gln Ile Ser Leu Pro Leu
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<210> 13
<211> 858
<212> DNA
<213> Homo sapiens

<400> 13

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<211> 285
<212> PRT
<213> Homo sapiens

<400> 14

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            20                  25                  30
Thr Gln Gly Ala Lys Ile Val Ser Leu Pro Glu Cys Phe Asn Ser Pro
        35                  40                  45
Tyr Gly Ala Lys Tyr Phe Pro Glu Tyr Ala Glu Lys Ile Pro Gly Glu
    50                  55                  60
Ser Thr Gln Lys Leu Ser Glu Val Ala Lys Glu Cys Ser Ile Tyr Leu
65                  70                  75                  80
Ile Gly Gly Ser Ile Pro Glu Glu Asp Ala Gly Lys Leu Tyr Asn Thr
                85                  90                  95
Cys Ala Val Phe Gly Pro Asp Gly Thr Leu Leu Ala Lys Tyr Arg Lys
            100                 105                 110
Ile His Leu Phe Asp Ile Asp Val Pro Gly Lys Ile Thr Phe Gln Glu
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        115                 120                 125
Ser Lys Thr Leu Ser Pro Gly Asp Ser Phe Ser Thr Phe Asp Thr Pro
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Tyr Cys Arg Val Gly Leu Gly Ile Cys Tyr Asp Met Arg Phe Ala Glu
145                 150                 155                 160
Leu Ala Gln Ile Tyr Ala Gln Arg Gly Cys Gln Leu Leu Val Tyr Pro
                165                 170                 175
Gly Ala Phe Asn Leu Thr Thr Gly Pro Ala His Trp Glu Leu Leu Gln
            180                 185                 190
Arg Ser Arg Ala Val Asp Asn Gln Val Tyr Val Ala Thr Ala Ser Pro
        195                 200                 205
Ala Arg Asp Asp Lys Ala Ser Tyr Val Ala Trp Gly His Ser Thr Val
    210                 215                 220
Val Asn Pro Trp Gly Glu Val Leu Ala Lys Ala Gly Thr Glu Glu Ala
225                 230                 235                 240
Ile Val Tyr Ser Asp Ile Asp Leu Lys Lys Leu Ala Glu Ile Arg Gln
                245                 250                 255
Gln Ile Pro Val Phe Arg Gln Lys Arg Asn Ile Phe Leu Asn Met Gln
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Date Mailed: January 25, 2001 Int'l. Appl. Ser. No.: to be assigned MPK

Applicant: Lexicon Genetics Incorporated

Title: Novel Human Enzymes and Polynucleotides Encoding the Same

Attorney Docket No.: LEX-0118-PCT

X Specification 28 pages total (26 pages spec; 1 claim page(s); 1 page Abstract)
X Request Form 5 pages
X Power of Attorney executed
X Fee Calculation Sheet
X Verified Statement executed
___ Drawings (___ pages; ___ number of drawings)
X Sequence Listing (8 pages; X machine-readable data carrier)
___ PCT-EASY diskette
Other: return postcard;

[redacted]

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Express Mail No.: EL 672756762 US
Date Mailed 1-25-01 U.S. Appl. Ser. No.: to be assigned
Inventors: Donahoe, Hilbun, Scoville, Turner, Friedrich, Abun, Zambrowicz, Sands
Title: Novel Human Enzymes + Polynucleotides Encoding the Same
Attorney Docket No.: LEX-0118-USA

X Specification 28 pages total (26 pages spec; 1 claim page(s); 1 page Abstr
X Transmittal Letter (original and copy)
___ Drawings (_____ pages; _____ number of drawings)
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Other: return postcard; unsigned Declaration